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Requestor's Name: Delacroix

Serial Number: 08/966,940

Date: 2/16/99 Phone: 306-3027 Art Unit: 1651
9803

Search Topic:
Please write a detailed statement of search topic. Describe specifically as possible the subject matter to be searched. Define any terms that may have a special meaning. Give examples or relevent citations, authors, keywords, etc., if known. For sequences, please attach a copy of the sequence. You may include a copy of the broadest and/or most relevent claim(s).

Please search the following:

1) A composition comprising tumor necrosis factor (TNFα) and a colloidal metal (gold or silver Au^{3+}, $HAuCl_4$ (gold chloride).

2) a vaccine comprising tumor necrosis factor (TNF- and a colloidal metal (gold, silver, Au^{3+}, $HAuCl_4$ → gold chlor and an adjuvant, specifically
→ Freund's complete adjuvant

Thanks
CM

STAFF USE ONLY

Date completed: 02-22-99
Searcher: Beverly C.9994
Terminal time: 25
Elapsed time:
CPU time:
Total time: 37
Number of Searches:
Number of Databases: 1

Search Site
- ____ STIC
- ____ CM-1
- ____ Pre-S

Type of Search
- ____ N.A. Sequence
- ____ A.A. Sequence
- ____ Structure
- ____ Bibliographic

Vendors
- ____ IG
- ✓ STN
- ____ Dialog
- ____ APS
- ____ Geninfo
- ____ SDC
- ____ DARC/Questel
- ____ Other

PTO-1590 (9-90)

Delacroix
08/966940

Key terms
Query 2

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     FILE 'REGISTRY' ENTERED AT 14:41:18 ON 22 FEB 1999
L1             0 SEA ABB=ON  PLU=ON  TUMOR NECROSIS FACTOR/CN
                 E TUMOR NECROSIS FACTOR/CN 5
L2           555 SEA ABB=ON  PLU=ON  TUMOR NECROSIS FACTOR ?/CN
                 E "TUMOR NECROSIS FACTOR-.ALPHA."/CN 5
L3             2 SEA ABB=ON  PLU=ON  ("TUMOR NECROSIS FACTOR-.ALPHA.
                 (HORSE REDUCED)"/CN OR "TUMOR NECROSIS FACTOR-.ALPHA.
                 (OX CLONE BGTNF3 PRECURSOR GENE TNFA)"/CN)
L4           556 SEA ABB=ON  PLU=ON  L2 OR L3
L5             5 SEA ABB=ON  PLU=ON  (GOLD OR SILVER OR GOLD CHLORIDE)/CN


     FILE 'CAPLUS' ENTERED AT 14:43:02 ON 22 FEB 1999
L6         29331 SEA ABB=ON  PLU=ON  L4 OR (TUMOUR OR TUMOR)(W)NECROSIS(W)
                 FACTOR OR TNF#(S)NECROSIS
L7            65 SEA ABB=ON  PLU=ON  L6 AND (L5 OR COLLOID?(2A)METAL OR
                 GOLD OR SILVER OR (AU OR AU3# OR AUCL# OR HAUCL#)(S)GOLD
                 OR AG(S)SILVER)
L8             4 SEA ABB=ON  PLU=ON  L7 AND (VACCIN? OR IMMUNIS? OR
                 IMMUNIZ? OR ADJUVANT)

L8   ANSWER 1 OF 4  CAPLUS  COPYRIGHT 1999 ACS
AN   1998:793064  CAPLUS
DN   130:35133
TI   P-selectin translocation to vascular epithelial lumen by ionizing
     radiation, and therapeutic use
IN   Hallahan, Dennis E.; Virudachalam, Subbulakshmi
PA   Arch Development Corporation, USA
SO   PCT Int. Appl., 178 pp.
     CODEN: PIXXD2
DT   Patent
LA   English
FAN.CNT 1
     PATENT NO.         KIND  DATE          APPLICATION NO.  DATE
     ---------------    ----  --------      ---------------  --------
PI   WO 9853852          A1   19981203      WO 98-US10913    19980529
         W:  AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ,
             DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP,
             KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK,
             MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL,
             TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG,
             KZ, MD, RU, TJ, TM
         RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK,
             ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF,
             CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG
PRAI US 97-48141      19970530
AB   The present invention relates to the use of P-selectin as a
     targeting agent in radiotherapies for vascular related disease.
     P-selectin is translocated to the lumen of vascular endothelia as a
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result of radiation. Thus, P-selecting provides a target for receptor-mediated delivery of drugs, including anticancer drugs and drugs for the treatment of vascular disease. However, P-selectin also plays a role in the activation of certain inflammatory cells and, as such, plays a role in radiation-induced inflammation. By interfering with P-selectin induction of inflammation, it is possible to modulate inflammatory responses to radiation therapy.

L8 ANSWER 2 OF 4 CAPLUS COPYRIGHT 1999 ACS
AN 1997:307639 CAPLUS
DN 126:282806
TI Antitumor agent from propolis extracts
IN Arai, Shigeyuki; Nishizaki, Yasushi; Kimoto, Tetsuo; Kurimoto, Masashi
PA Kabushiki Kaisha Hayashibara Seibutsu Kagaku Kenkyujo, Japan
SO Brit. UK Pat. Appl., 23 pp.
CODEN: BAXXDU
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	GB 2302809	A1	19970205	GB 96-14079	19960704
	JP 09071528	A2	19970318	JP 96-177237	19960619
	US 5710179	A	19980120	US 96-675059	19960703
PRAI	JP 95-191015		19950705		

AB An antitumor agent comprises as an effective ingredient 3-[4-hydroxy-3,5-bis(3-methyl-2-butenyl)phenyl]-2-propenoic acid (I) and/or its physiol. acceptable salt(s). The agent exerts a strong antitumor activity without substantially inducing side effects. I was isolated from the EtOAc exts. of propolis mass and salts of Na, K, Mg, Ca were prepd. Antitumor activities of I and salts were tested in Meth A sarcoma cell-bearing mice. Formulations for tablets, capsules, injections, topicals, suppositories contg. I, are provided.
IT **7440-57-5D, Gold**, compds.
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antitumor compns. contg. phenylpropenoate deriv. from propolis exts. and addnl. agents)

L8 ANSWER 3 OF 4 CAPLUS COPYRIGHT 1999 ACS
AN 1995:430885 CAPLUS
DN 122:230316
TI **Gold** salts modify the Th1-Th2 balance in experimental autoimmune uveoretinitis (EAU)
AU Sheela, R.; Saoudi, A.; Kozak, Y. de; Huygen, K.; Druet, P.; Bellon, B.
CS INSERM U28, Hopital Broussais, Paris, 75674, Fr.

SO Int. Congr. Ser. (1994), 1068(Advances in Ocular Immunology), 259-62
CODEN: EXMDA4; ISSN: 0531-5131
DT Journal
LA English
AB **Gold** compds., used in rheumatoid arthritis (RA) therapy, are known to trigger adverse immune reactions related to T helper (Th) 2 response in certain patients. Since RA is presumed to be a Th1 dependent disease, **gold** salts may act by skewing the immune response towards Th2 type. In this study we analyzed the effect of **gold** salts in the development of Th1 mediated exptl. autoimmune uveoretinitis induced by retinal S antigen (SAg) in (Lewis X Brown Norway)F1 rats. **Immunization** of F1 rats on day 7 after the first injection with **gold** salts induced a clearcut Th2 response. Prodn. of IL-4 was increased while that of IL-2, IFN-.gamma. and TNF-.alpha. were reduced in in vitro cultures of spleen and lymph node cells from **gold** salt-treated SAg **immunized** rats (**Au**-SAg); concomitantly, prodn. of nitric oxide was reduced in these rats. Anal. of the isotypes of anti-SAg antibodies showed that IgG1 levels were significantly elevated in Au-SAg rats, while the levels of IgG2a was significantly elevated in the H2O-SAg rats. No significant clin. protection was obsd. in **gold** salts treated rats, as against the complete protection obsd. after treatment with HgCl2, another Th2 activating chem. One of the possible reasons for this lack of protection may be that **gold** salt-induced Th2 response is not strong enough to protect completely against this Th1 mediated disease. But under mild disease conditions this skewing of the immune response from Th1 to Th2 may be sufficient enough to contain the disease.
IT **7440-57-5D**, **Gold**, compds.
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**gold** salts modify Th1-Th2 balance in autoimmune uveoretinitis)

L8 ANSWER 4 OF 4 CAPLUS COPYRIGHT 1999 ACS
AN 1994:663724 CAPLUS
DN 121:263724
TI **Metal colloids** for reducing toxicity of biologically active factors
IN Tamarkin, Lawrence; Paciotti, Giulio Franco
PA Assay Research, Inc., USA
SO PCT Int. Appl., 27 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9421288	A1	19940929	WO 94-US3177	19940318

Searcher : Shears 308-4994

W: AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, KZ, LK, LU, LV, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA, UZ, VN
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG

CA 2158475	AA	19940929	CA 94-2158475	19940318
AU 9464149	A1	19941011	AU 94-64149	19940318
EP 690722	A1	19960110	EP 94-911691	19940318
R: AT, DE, FR, GB, IT				
JP 08511236	T2	19961126	JP 94-521360	19940318
PRAI US 93-33385	19930318			
WO 94-US3177	19940318			

AB A biol. active factor is admixed with a **colloidal metal** (e.g. Au, Ag) prior to administration to a human or animal to prevent toxic side effects of the factor. This compn. can be used to treat a disease with a biol. active factor (e.g. IL-2 or IL-6) or to safely **vaccinate** a human or animal against a biol. active factor.

IT **7440-22-4**, **Silver**, biological studies
7440-57-5, **Gold**, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**colloidal**; **metal colloids** for reducing toxicity of biol. active factors)

=> d his l9-; d 1-23 bib abs

(FILE 'BIOSIS, MEDLINE, EMBASE, LIFESCI, BIOTECHDS, WPIDS, CONFSCI, SCISEARCH, JICST-EPLUS, PROMT, TOXLIT, TOXLINE, DRUGU, DRUGNL, DRUGB' ENTERED AT 14:47:59 ON 22 FEB 1999)

L9 23 S L8
L10 15 DUP REM L9 (8 DUPLICATES REMOVED)

L10 ANSWER 1 OF 15 PROMT COPYRIGHT 1999 IAC

AN 1999:69843 PROMT
TI CAPECITABINE (Roche) Xeloda FDA rating 1-P.(includes related information on other drugs)
SO Drug Topics, (1 Feb 1999) Vol. 143, No. 2, pp. 58(1).
ISSN: 0012-6616.
PB Medical Economics Company, Inc.
DT Newsletter
LA English
WC 9537
FULL TEXT IS AVAILABLE IN THE ALL FORMAT
AB Capecitabine is a fluoropyrimidine carbamate prodrug that is administered orally to serve as a systemic prodrug for 5-fluorouracil (5-FU), still one of the most prescribed cytostatic drugs. It is transformed to the active agent, 5-FU, which then acts

both as antimetabolite and by counterfeit incorporation to hinder both DNA and RNA functions in cell proliferation.
THIS IS THE FULL TEXT: COPYRIGHT 1999 Medical Economics Publishing

L10 ANSWER 2 OF 15 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.
AN 1998235212 EMBASE
TI New prospects for the treatment of rheumatoid arthritis.
AU Choy E.H.S.
CS E.H.S. Choy, Clinical/Academic Rheumatology Unit, King's College Hospital, East Dulwich Grove, London SE22 8PT, United Kingdom. e.choy@umds.ac.uk
SO Expert Opinion on Investigational Drugs, (1998) 7/7 (1087-1097).
Refs: 75
ISSN: 1354-3784 CODEN: EOIDER
CY United Kingdom
DT Journal; General Review
FS 026 Immunology, Serology and Transplantation
030 Pharmacology
031 Arthritis and Rheumatism
037 Drug Literature Index
038 Adverse Reactions Titles
LA English
SL English
AB Rheumatoid arthritis (RA) is a common inflammatory and destructive arthropathy. Current therapies fail to stop joint damage and reduce long-term disability. Greater understanding of disease pathogenesis has identified many inflammatory mediators as possible therapeutic targets. Novel therapeutic agents, such as monoclonal antibodies (mAbs), cytokine receptor-human immunoglobulin constructs, recombinant human proteins and antisense oligodeoxynucleotides targeting these inflammatory mediators have been tested in rheumatoid arthritis with some success. In particular, inflammation can be effectively suppressed using anticytokine therapies. However, the ideal treatment for RA, one that is immunomodulatory and induces prolonged disease remission after a single course of therapy, still eludes us. Strategies aiming to achieve this include TCR peptide **vaccination** and anti-CD4 mAbs, currently in clinical trials in RA.

L10 ANSWER 3 OF 15 BIOSIS COPYRIGHT 1999 BIOSIS
AN 1998:460204 BIOSIS
DN PREV199800460204
TI Modulation of some cytokines expression by **gold** or methotrexate in **adjuvant** arthritis.
AU Hulejova, H. (1); Martinek, J.; Adam, M. (1)
CS (1) Inst. Rheumatol., Charles Univ., Prague Czech Republic
SO Reumatologia (Warsaw), (1998) Vol. 36, No. SUPPL., pp. 156.
Meeting Info.: 2nd Central European Congress of Rheumatology Warsaw, Poland May 13-16, 1998

ISSN: 0034-6233.
DT Conference
LA English

L10 ANSWER 4 OF 15 SCISEARCH COPYRIGHT 1999 ISI (R)
AN 97:90620 SCISEARCH
GA The Genuine Article (R) Number: WD152
TI Mononuclear phagocytes and rheumatoid synovitis - Mastermind or workhorse in arthritis?
AU Burmester G R (Reprint); Stuhlmuller B; Keyszer G; Kinne R W
CS HUMBOLDT UNIV BERLIN, DEPT MED 3, CHARITE UNIV HOSP, SCHUMANNSTR 20-21, D-10117 BERLIN, GERMANY (Reprint); UNIV LEIPZIG, INST CLIN IMMUNOL & TRANSFUS MED, D-7010 LEIPZIG, GERMANY
CYA GERMANY
SO ARTHRITIS AND RHEUMATISM, (JAN 1997) Vol. 40, No. 1, pp. 5-18. Publisher: LIPPINCOTT-RAVEN PUBL, 227 EAST WASHINGTON SQ, PHILADELPHIA, PA 19106.
ISSN: 0004-3591.
DT General Review; Journal
FS LIFE; CLIN
LA English
REC Reference Count: 177

L10 ANSWER 5 OF 15 BIOSIS COPYRIGHT 1999 BIOSIS
AN 1996:312760 BIOSIS
DN PREV199699035116
TI Cardiac myosin-induced myocarditis: Target recognition by autoreactive T cells requires prior activation of cardiac interstitial cells.
AU Pummerer, Christian L.; Graessl, Gerhard; Sailer, Michaela; Bachmaier, Kurt W.; Penninger, Josef M.; Neu, Nikolaus
CS Univ. Klinik fuer Kinderheilkunde, Anichstrasse 35, A-6020 Innsbruck Austria
SO Laboratory Investigation, (1996) Vol. 74, No. 5, pp. 845-852.
ISSN: 0023-6837.
DT Article
LA English
AB **Immunization** with cardiac myosin causes T cell-mediated myocarditis in genetically predisposed mice and serves as a model for autoimmune heart disease. The normal heart is not susceptible to T cells autoreactive with cardiac myosin; therefore, we investigated the conditions that are required to facilitate recognition of the target tissue. A.SW mice were **immunized** with cardiac myosin on Days 0 and 7. Major histocompatibility antigen (MHC Ag) and intercellular adhesion molecule-1 (ICAM-1) expression in the heart tissue was investigated by immunohistochemical techniques shortly before disease onset (ie, on Day 9). At this time point, cardiac interstitial cells expressing class II but not class I MHC Ag were significantly increased. In addition, endothelial ICAM-1

expression was strongly up-regulated. Myofibers did not show expression of these markers, and T cells were virtually absent. Because lipopolysaccaride (LPS) induced a similar distribution of class II MHC Ag and ICAM-1 in the myocardial tissue and because these molecules could be crucial to disease onset, we determined whether treatment with this immunomodulator renders the heart susceptible to passively transferred myosin-reactive T cells. We found that concanavalin A-activated spleen cells from myosin-**immunized** donors induced myocarditis in LPS-primed recipients, whereas normal mice were resistant to the injection of such cells. Increased class II MHC Ag expression after LPS-treatment was mediated by TNF because LPS-primed mice genetically lacking the TNF receptor failed to increase class II MHC Ag expression in the heart tissue. In summary, these results suggest that in cardiac myosin-induced myocarditis, expression of interstitial class II MHC Ag and/or endothelial ICAM-1 is a prerequisite for target organ recognition by autoreactive T cells.

L10 ANSWER 6 OF 15 PROMT COPYRIGHT 1999 IAC

AN 97:9741 PROMT
TI Centocor's brighter days
SO Med Ad News, (Dec 1996) pp. 25.
ISSN: 0745-0907.
LA English
WC 1315
FULL TEXT IS AVAILABLE IN THE ALL FORMAT
AB The storm has passed. David Holveck and the rest of the management team have guided Centocor Inc. to safety. After an extremely difficult period that lasted about three years, the 16-year-old biotechnology company has one promising product on the market and the ability to deliver more. After a complete restructuring and a new business strategy, the company is on its way to commercialization and profitability.
Before 1993, Centocor's managers, like most other biotechnology chiefs, wanted to be completely independent. Originally, Centocor's managers wanted what every other biotech manager wanted: to build a fully integrated bio-pharmaceutical company. They planned to establish their own sales force and marketing force and own the rights to their products around the world.
'There's nothing wrong with that strategy,' Mr. Holveck says. 'but we built the infrastructure prior to having a product approved. When Centoxin didn't get approved, we had nothing else to put into the infrastructure.'
Centoxin, a promising investigational drug that would have treated septic shock for the first time back in 1993, elevated the company to superstardom. But as quickly as Centocor was lifted, the company fell. While in clinical trials, an excess of mortality among patients treated with the product was reported. The drug's clinical

development was suspended in the United States. Already approved in Europe, the product was pulled off that market.
But since that time, a new strategy was devised, calling for smart partnership arrangements. Centocor's managers had to decide how to move forward. They decided to find big pharmaceutical companies to be their corporate partners. These partners would take to market the drugs discovered by Centocor.

L10 ANSWER 7 OF 15 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.
AN 94339223 EMBASE
DN 1994339223
TI **Gold** sodium thiomalate down-regulates intercellular adhesion molecule-1 and vascular cell adhesion molecule-1 expression on vascular endothelial cells.
AU Koike R.; Miki I.; Otoshi M.; Totsuka T.; Inoue H.; Kase H.; Saito I.; Miyasaka N.
CS Division of Immunological Diseases, Medical Research Institute, Tokyo Medical and Dental University, 1-5-45, Yushima,Bunkyo-ku, Tokyo, Japan
SO Molecular Pharmacology, (1994) 46/4 (599-604).
ISSN: 0026-895X CODEN: MOPMA3
CY United States
DT Journal; Article
FS 030 Pharmacology
031 Arthritis and Rheumatism
037 Drug Literature Index
LA English
SL English
AB We examined whether antirheumatic drugs alter cytokine- or lipopolysaccharide-induced expression of adhesion molecules on vascular endothelial cells. Human umbilical cord vein endothelial cells were co- cultured with various antirheumatic drugs in the presence of inflammatory cytokines, and adhesion molecule expression was measured by cell enzyme- linked immunosorbent assay and Northern blot analysis. Among these antirheumatic drugs, **gold** sodium thiomalate significantly inhibited intercellular adhesion molecule-1 and vascular cell adhesion molecule-1 expression on vascular endothelial cells and suppressed cellular binding between human monocytic cell lines, including U937 and HL-60 cells, and interleukin-1.beta.-stimulated vascular endothelial cells. It is speculated that down-regulation of adhesion molecules might be one of the novel mechanisms of action of **gold** sodium thiomalate.

L10 ANSWER 8 OF 15 MEDLINE DUPLICATE 1
AN 95015975 MEDLINE
DN 95015975
TI Interleukin-8 production is regulated by protein kinase C in human

keratinocytes.
AU Chabot-Fletcher M; Breton J; Lee J; Young P; Griswold D E
CS Department of Inflammation Pharmacology, SmithKline Beecham Pharmaceuticals, King of Prussia, Pennsylvania 19406..
SO JOURNAL OF INVESTIGATIVE DERMATOLOGY, (1994 Oct) 103 (4) 509-15. Journal code: IHZ. ISSN: 0022-202X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199501
AB Interleukin-8 (IL-8) is a potent pro-inflammatory molecule present in high amounts in psoriatic skin. Here it may play an important role in the keratinocyte hyperproliferation and the neutrophil and T-lymphocyte infiltration associated with the disease. In this study the effect of protein kinase C inhibitors on IL-8 production by human keratinocytes in vitro was investigated. The anti-inflammatory and immunomodulatory compound auranofin ([1-thio-beta-D-glucopyranose-2,3,4,6-tetraacetato-S] [triethylphosphine] **gold**) is known to inhibit protein kinase C. In addition, auranofin has been shown to inhibit skin inflammation. As such, auranofin was also studied for its effect on IL-8 production. Auranofin and staurosporine, inhibitors of protein kinase C, inhibited phorbol-myristate-acetate-stimulated IL-8 production. Northern analysis of IL-8 mRNA revealed that the inhibition of IL-8 production was associated with an inhibition of IL-8 mRNA expression. In contrast, these compounds potentiated the minimal IL-8 protein and mRNA seen in response to interleukin-1 beta or **tumor necrosis factor**-alpha. These findings suggest that IL-8 synthesis may be either positively or negatively regulated by protein kinase C depending on the stimulus.

L10 ANSWER 9 OF 15 TOXLINE
AN 1995:250828 TOXLINE
DN IPA-95-1067312
TI Clinical pharmacology and modification of autoimmunity and inflammation in rheumatoid disease.
CM Review
AU Luqmani R; Gordon C; Bacon P
CS Dept. of Rheumatol., Univ. of Birmingham, Vincent Dr., Edgbaston, Birmingham B15 2TT, England.
SO Drugs, (1994). Vol. 47, Feb, pp. 259-285 (REF 223). CODEN: DRUGAY. ISSN: 0012-6667.
FS IPA
LA English
OS IPA 32-1067312
EM 199509
AB IPA COPYRIGHT: ASHP A review of conventional slow-acting antirheumatic drugs for modification of autoimmunity and

inflammation in rheumatoid disease is presented, including an overview of the clinical response and toxicity of antimalarials, sulfasalazine, **gold** salts, penicillamine, corticosteroids, methotrexate, cyclosporine (cyclosporin), azathioprine, cyclophosphamide, and chlorambucil. Specific immunological therapy with monoclonal antibodies, peptide therapy, T cell **vaccination**, interference with the cytokine network, TNFalpha inhibitors, and intravenous immunoglobulins is also discussed.

L10 ANSWER 10 OF 15 DRUGU COPYRIGHT 1999 DERWENT INFORMATION LTD
AN 94-10000 DRUGU T E
TI Current and Future Therapeutic Strategies for Rheumatoid Arthritis (RA).
AU Schact E
CS Tosse
LO Hamburg, Germany,West
SO Z.Rheumatol. (52, No. 6, 365-82, 1993) 8 Fig. 197 Ref.
CODEN: ZRHMBQ ISSN: 0340-1855
AV Leiter der Hauptabteilung, Medizinische Wissenschaften, E. Tosse and Co. GmbH, Friedrich-Ebert-Damm 101, 22047, Hamburg, Germany.
LA German
DT Journal
FA AB; LA; CT
FS Literature
AN 94-10000 DRUGU T E
AB Rheumatoid arthritis (RA) is reviewed with reference to the involvement of inflammation, immunoproliferation and synovial hyperplasia in the disease process, the use of NSAID, steroids and other drugs to inhibit inflammation, combined use of drugs including methotrexate, parenteral **gold**, sulfasalazine (salazosulfapyridine), antimalarials such as hydroxychloroquine, and azathioprine to antagonize the disease-process, modern therapies based on modulation of the immune system, and peroral delivery of antigens (PAD) in the treatment of autoimmune diseases. Effects of cytokines and IFN-gamma on RA and the predictive value of differential diagnosis for the success of therapy are also discussed.
ABEX Steroids (prednisolone) and inhibitors of PG synthesis including NSAID, misoprostol and benoxaprofen can be used to inhibit inflammation without affecting the underlying cause of RA. New approaches include the use of clozic and bradykinin-, histamine-, substance P- or calcitonin gene-related peptide CGRP-antagonists. Capsaicin interferes with the activity of substance P. Tissue inflammation involves cytokines and adhesion molecules, and synthetic monosaccharides such as amiprilose HCl have anti-inflammatory effects. Disease-modifying therapeutics include **gold**, methotrexate, sulfasalazine, penicillamine, azathioprine, antimalarials and OM-8980 (Subreum). Combination of

an antimalarial with azathioprine and low-dose methotrexate is more effective and better tolerated than cyclophosphamide triple-therapy. Recent therapies aim to interfere with RA by inhibiting T-cells with monoclonal Ab against T-cell surface antigens, inhibiting IL-2 gene expression, or inhibiting T-cell activation with ciclosporin, or FK-506 or Ab against IL-2 receptors. TNF-alpha-blockers and T-cell **vaccination** have also been used. T-cell activation can be modulated with MHC-blocked peptides, Ab against MHC-antigens or peptides analogous to T-cell receptor-sequences, or vitamin D-metabolites (1,25-vitamin D3). Antigens used in PAD include myelin basic protein (for multiple sclerosis), collagen II, HSP and proteoglycans (for RA), S-antigens (uveitis) and pancreatic islet tissue (insulin-dependent diabetes). (S67/AS) (Gegenwaertige und zukuenftige Therapiestrategien der rheumatoiden Arthritis (RA))

L10 ANSWER 11 OF 15 BIOSIS COPYRIGHT 1999 BIOSIS DUPLICATE 2
AN 1993:523684 BIOSIS
DN PREV199396137091
TI Humoral immune responses in volunteers **immunized** with irradiated Plasmodium falciparum sporozoites.
AU Egan, James E.; Hoffman, Stephen L.; Haynes, J. David; Sadoff, Jerald C.; Schneider, Imogene; Grau, George E.; Hollingdale, Michael R.; Ballou, W. Ripley; Gordon, Daniel M. (1)
CS (1) Dep. Immunol., Walter Reed Army Inst. Res., Washington, DC 20307-5100 USA
SO American Journal of Tropical Medicine and Hygiene, (1993) Vol. 49, No. 2, pp. 166-173.
ISSN: 0002-9637.
DT Article
LA English
AB Volunteers **immunized** with gamma-irradiated Plasmodium falciparum sporozoites serve as the **gold** standard for protective immunity against mosquito-borne malaria transmission and provide a relevant model for studying protective immune effector mechanisms. During a 7-12-month period, we **immunized** four volunteers via the bites of irradiated, infected mosquitoes. Following these exposures to attentuated sporozoites, all four volunteers developed antibodies to sporozoites as measured by an immunofluorescence assay and by an enzyme-linked immunosorbent assay using the circumsporozoite (CS) protein repeat-based molecule R32LR as capture antigen. Three volunteers also developed antibodies against the nonrepeating (flanking) regions of the CS protein; the level of these antibodies paralleled the serum activity to inhibit sporozoite invasion of hepatoma cells in vitro. These three volunteers were protected against malaria transmitted by the bites of five infected mosquitoes. Two of these protected volunteers received additional **immunizing** doses of irradiated sporozoites and were subsequently protected against challenge with a

heterologous P. falciparum clone. No detectable fluctuations were observed in circulating levels of **tumor necrosis factor**, interferon-gamma, or interleukin-6 during the course of this study. Analysis of the humoral and cellular immune responses of these protected volunteers is expected to yield important clues to additional targets of immunity against the pre-erythrocytic stages of malaria parasites.

L10 ANSWER 12 OF 15 DRUGU COPYRIGHT 1999 DERWENT INFORMATION LTD
AN 93-14024 DRUGU G
TI Quantitation of E.coli Protein Impurities in Recombinant Human Interferon-Gamma.
AU Chen A B; Championsmith A A; Blanchard J; Gorrell J; Niepelt B A; Federici M M
CS Genentech
LO South San Francisco, California, United States
SO Appl.Biochem.Biotechnol. (36, No. 2, 137-52, 1992) 5 Fig. 7 Tab. 16 Ref.
CODEN: ABIBDL ISSN: 0273-2289
AV Department of Medicinal and Analytical Chemistry, Genentech, Inc., M/S 38, 460 Point San Bruno Blvd., South San Francisco, CA 94080, U.S.A. (Sinicropi D V, 8 authors).
LA English
DT Journal
FA AB; LA; CT
FS Literature
AN 93-14024 DRUGU G
AB E. coli protein (ECP) impurities were detectable during the purification process, but were undetectable in 3 purified lots of recombinant IFN-gamma (IFNg, Actimmune; Genentech) using an ELISA assay with antibodies raised in rabbits. ECP reactivity was increased by IFNg, poly-lysine, cytochrome-c, histone and nerve-growth-factor, but not neutral or acidic proteins.
ABEX Methods Anti-ECP antibodies were raised in rabbits given ECP (0.5 mg s.c.) in complete Freunds **adjuvant** followed by 3-wkly boosters of 0.25 mg in incomplete **adjuvant**.
Results The majority of bands on SDS-PAGE analysis of the ECP standard which were detected by **silver** staining were also demonstrable by immunoblotting. IFNg bands blotted with anti-IFNg, but not anti-ECP antibodies. An ELISA for ECP in IFNg samples was set up; immunoreactivity of the ECP standard was enhanced by IFNg (0.5-200 ug/ml). 3 Lots of IFNg contained no detectable amount of ECP. The limit of detection of the assay was 1.3 ng ECP; the intra- and inter-assay % coefficients of variation were 3% and 3.3%, respectively. ECP were detected in in-process samples of IFNg, the number of bands declining with the progression of the process. ECP specific to the processes for the purification of human GH (somatotropin), TNF-alpha and tissue-factor showed less than 0.31% cross-reactivity with that derived from IFNG

Searcher : Shears 308-4994

purification. Reactivity of the ECP was increased by IFNg, poly-lysine, cytochrome-c, histone and nerve-growth-factor but not neutral or acidic proteins or protamine. (W76/AE)

L10 ANSWER 13 OF 15 DRUGU COPYRIGHT 1999 DERWENT INFORMATION LTD
AN 92-13974 DRUGU T
TI Intravesical **Adjuvant** Treatment in Superficial Bladder Cancer: A Review of the Question After 15 Years of Experience with the EORTC GU Group.
AU Bouffioux C
LO Liege, Belgium
SO Scand.J.Urol.Nephrol. (Suppl. 138, 167-77, 1991) 1 Fig. 11 Tab. 54 Ref.
CODEN: SJUNAS ISSN: 0036-5599
AV Department of Urology, University Hospital Liege, Liege, Belgium.
LA English
DT Journal
FA AB; LA; CT
FS Literature
AN 92-13974 DRUGU T
AB Intravesicular therapy for superficial bladder cancer is reviewed. Intravesicular instillation of a therapeutic agent is used for chemoresection, where the agent is given with immediate therapeutic intent, and for chemoprophylaxis, where the agent is given to prevent or delay recurrence and reduce the risk of invasive disease following transurethral resection (TUR) of visible tumors. BCG, mitomycin-C (MMC) and Adriamycin (ADM) have been used successfully for chemoresection of carcinoma in situ (CIS). Various trials of **adjuvant** intravesicular treatment after TUR (chemoprophylaxis), mainly EORTC studies, have demonstrated the efficacy of MMC, thiotepa and BCG. Current studies involve sequential BCG and MMC, BCG alone and with p.o. isoniazid, epirubicin, IFN, interleukins, TNF, mitoxantrone, KHL + **adjuvant** therapy.
ABEX Since the 1st report of intravesicular instillation of **silver** nitrate in 1903, at least 35 agents have been used for the treatment of superficial bladder cancer. ADM, Epodyl, MMC and epidoxorubicin have proved effective with low systemic toxicity, while thiotepa, cisplatin and BCG are effective but may produce severe systemic toxicity. Cystoprostatectomy (+ urethrectomy) is the most radical treatment for CIS but instillation of MMC, ADM or BCG has become a more usual treatment in the last 10 yr and generally, BCG appears superior to MMC or ADM. Various trials of **adjuvant** intravesicular therapy following TUR have demonstrated the efficacy of thiotepa, ADM, Epodyl and MMC, but not VM26, in reducing recurrence rates. Cisplatin is also effective but is not recommended because of the risk of anaphylactic reaction. Toxicity of MMC, ADM and Epodyl is generally minor and includes local toxicity (chemical cystitis),

thrombocytopenia and mild systemic side-effects (pruritis, vertigo, nausea). The time of initiation of MMC instillation (immediately after TUR vs. within 10 days) and the duration of treatment (6 mth vs. 12 mth) does not affect the recurrence rate but delayed, short-term ADM therapy appears the least favorable protocol. A single instillation of epirubicin on the day of TUR improves recurrence rates for low-risk superficial tumors. BCG is effective as **adjuvant** therapy but its superiority over MMC or ADM has not been established; various strains of BCG (RIVM, Connaught, Tice, Pasteur) appear similarly effective and similarly toxic. Local and systemic toxicity of BCG exceeds that of the chemotherapeutic agents and delayed treatment after TUR is essential. (W2/AE)

L10 ANSWER 14 OF 15 BIOSIS COPYRIGHT 1999 BIOSIS DUPLICATE 3
AN 1990:332299 BIOSIS
DN BA90:40318
TI EOSINOPHIL CYTOTOXICITY ENHANCING FACTOR PURIFICATION CHARACTERIZATION AND IMMUNOCYTOCHEMICAL LOCALIZATION ON THE MONOCYTE SURFACE.
AU ELSAS P X; ELSAS M I C G; DESSEIN A J
CS SERV. IMUNOHEMATOLOGIA, HOSP. EVANDRO CHAGAS, INST. OSWALDO CRUZ, FIOCRUZ, AV. BRASIL 4365, CEP 21040, RIO DE JANEIRO, BRAZIL.
SO EUR J IMMUNOL, (1990) 20 (5), 1143-1152.
CODEN: EJIMAF. ISSN: 0014-2980.
FS BA; OLD
LA English
AB The monokine eosinophil cytotoxicity enhancing factor (ECEF) increases antibody-dependent cytotoxicity of eosinophils towards helminth larvae. A monokine biochemically indistinguishable from ECEF increases the release of leukotriene C4 and other arachidonic acid metabolites by eosinophils. We have developed monoclonal antibodies (mAb) to these monokines by **immunizing** mice with ECEF made by the U-937 histiocytic lymphoma cell line. mAb 81.10.C9 (IgG2b) and 9A6G (IgG1) inhibit the effect of the monokine on release of AA products. Both mAb bind ECEF, which appears after affinity chromatography purification as a major 13-14-kDa and a minor 62-kDa component (13-14 kDa and 52 kDa after reduction) in **silver**-stained gels. An additional component of 30 kDa is detectable after radioiodination of the immunopurified material. The specificity of both mAb was studied in several ways. In immunoprecipitation, both recognize the 13-14-kDa and the 30-kDa components, while the 62-(52)-kDa protein is not significantly precipitated. Both mAb react in enzyme-linked immunosorbent assay with products secreted by peripheral blood mononuclear cells and monocytes, as well as with those secreted by phorbol 12-myristate 13-acetate and lipopolysaccharide-stimulated U-937 cells and with the immunopurified proteins. These were separated in sodium dodecyl sulfate-polyacrylamide gel electrophoresis, electroeluted and

assayed for ECEF activity. Activity was associated with the 13-14-kDa and the 30 kDa fractions, as seen by increased eosinophil antibody-dependent adherence to schistosomula and cytotoxicity. Granulocyte-monocyte-colony-stimulating factor and interleukin 1, but not **tumor necrosis factor**, could be detected in crude U-937 supernatants. However, active immunopurified ECEF has no activity in assays for granulocyte-monocyte-colony-stimulating factor, interleukin 1 or **tumor necrosis factor**. Immunocytochemical localization of ECEF employing the mAb shows strong surface staining of viable monocytes and U-937 cells, suggesting that ECEF is associated to the cell surface. These properties distinguish ECEF from other monokines previously reported to activate eosinophils.

L10 ANSWER 15 OF 15 MEDLINE
AN 87294384 MEDLINE
DN 87294384
TI [Current therapy: immunopharmaceuticals].
Aktuelle Therapie: Immunopharmaka.
AU Mahrle G
SO ZEITSCHRIFT FUR HAUTKRANKHEITEN, (1987 May 15) 62 (10) 753-6, 759-62, 765.
Journal code: XVK. ISSN: 0301-0481.
CY GERMANY, WEST: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
LA German
FS Priority Journals
EM 198711
AB Immunopharmarca are classified as follows: thymus factors and hormones, lymphokines and cytokines, microbial products, drugs with potential effects on the immune system, and external immunomodulators. We discuss new drugs and substances such as Timunox, Tp-1 Serono, delimmun, Isoprenosine, recombinant interleukin 2, Immuneron, **tumor necrosis factor**, Sandimmun, and diphencyprone, as well as drugs already known like Levamisole, Bestatin, **gold**, sulfones, and sulfopyridines.

=> d his l12- ful; d 1-17 .bevstr

Query 1

(FILE 'CAPLUS' ENTERED AT 14:55:01 ON 22 FEB 1999)
L12 19 SEA ABB=ON PLU=ON L6(S)(L5 OR COLLOID?(2A)METAL OR GOLD OR SILVER OR (AU OR AU3# OR AUCL# OR HAUCL#)(S)GOLD OR AG(S)SILVER)
L13 17 SEA ABB=ON PLU=ON L12 NOT L8

L13 ANSWER 1 OF 17 CAPLUS COPYRIGHT 1999 ACS

AN 1998:475908 CAPLUS
DN 129:201966
TI The tumor necrosis factor family of receptors/ligands in the serum of patients with rheumatoid arthritis
AU Robak, Tadeusz; Gladalska, Anna; Stepien, Henryk
CS Department of Hematology, Medical Univ. of Lodz, Lodz, 93-513, Pol.
SO Eur. Cytokine Network (1998), 9(2), 145-154
CODEN: ECYNEJ; ISSN: 1148-5493
PB John Libbey Eurotext
DT Journal
LA English
AB The authors investigated the serum concn. of the tumor necrosis factor (TNF) family ligands (TNF-.alpha. and TNF-.beta.) and their sol. receptors (sTNF-R p55 and sTNF-R p75) in 66 patients with rheumatoid arthritis (RA) and 14 healthy subjects as a control group, using an ELISA. The authors examd. a possible assocn. between the serum levels of these proteins and RA activity according to the Mallya & Mace scoring system and Ritchie's index. The authors also evaluate the correlation between the serum levels of ligands and their sol. receptors as well as the ligands and receptors concn. and the duration of the disease. TNF-.alpha., sTNF-R p55 and sTNF-R p75 were detectable in the serum of all 66 patients and 14 healthy individuals. In contrast, TNF-.beta. was measurable in only 14 (21.9%) patients with RA and in none of the control subjects. The highest TNF-.alpha., sTNF-R p55 and sTNF-R p75 levels were found in those patients in stage 4 of the disease, and the lowest in the control group. The authors found a pos. correlation between sTNF-R p55 and sTNR-R p75 serum levels correlated pos. with the duration of the disease, but levels of TNF-.beta. did not. The authors obsd. a pos. correlation between the concns. of TNF-.alpha. with sTNF-R p55 and with sTNF-R p75, as well as between both sol. receptors. In contrast, the authors have not obsd. any correlation between the serum level of TNF-.beta. with TNF-.alpha., sTNF-R p55, and sTNF-R p75. These studies indicate that TNF-.alpha., sTNF-R p55 and sTNF-R p75, but not TNF-.beta. (lymphotoxin .alpha.) are good markers of RA activity and that these proteins play an important role in the pathogenesis of this disease.
IT **7440-57-5D, Gold**, salts
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**tumor necrosis factors** and sol. receptors in serum of humans with rheumatoid arthritis in relation to treatment with)

L13 ANSWER 2 OF 17 CAPLUS COPYRIGHT 1999 ACS
AN 1997:703193 CAPLUS
DN 128:2660
TI NF-.kappa.B as a frequent target for immunosuppressive and anti-inflammatory molecules
AU Baeurle, Patrick A.; Baichwal, Vijay R.

CS Tularik Incorporated, South San Francisco, CA, 94080, USA
SO Adv. Immunol. (1997), 65, 111-137
CODEN: ADIMAV; ISSN: 0065-2776
PB Academic
DT Journal; General Review
LA English
AB A review with more than 100 refs. Topics discussed include glucocorticoids; cyclosporin A and FK506; rapamycin; salicylates; antioxidants; anti-**tumor necrosis factor** -.alpha. antibodies and **gold** compds. in treatment of rheumatoid arthritis; immunosuppressive activity of cAMP; spergualin; gliotoxin; and viral strategies to control NF-.kappa.B.

L13 ANSWER 3 OF 17 CAPLUS COPYRIGHT 1999 ACS
AN 1997:686003 CAPLUS
DN 127:326190
TI Sesame oil in injectable gold: two drugs in one?
AU Wolde, S. Ten; Engels, F.; Miltenburg, A. M. M.; Kuijpers, E. A. P.; Struijk-Wielinga, G. I.; Dijkmans, B. A. C.
CS Department of Rheumatology, University Hospital Leiden, Leiden, 2300 RC, Neth.
SO Br. J. Rheumatol. (1997), 36(9), 1012-1015
CODEN: BJRHDF; ISSN: 0263-7103
PB Oxford University Press
DT Journal
LA English
AB To investigate the potential anti-inflammatory effects of sesame oil, which is present in the injectable **gold** prepn. Auromyose, the synthesis of **tumor necrosis factor** alpha (**TNF**-.alpha.), prostaglandin E2 (PGE2) and leukotriene B4 (LTB4) by in vitro stimulated blood cells was measured before, during, and after 12 wk of dietary supplementation with 18 g of sesame oil daily in 11 healthy male volunteers. Neither TNF-.alpha., PGE2 nor LTB4 prodn. levels showed statistically significant changes during the 12 wk of dietary supplementation with sesame oil. These results do not suggest an anti-inflammatory effect of sesame oil as present in injectable gold prepns. which are used in the treatment of rheumatoid arthritis.

L13 ANSWER 4 OF 17 CAPLUS COPYRIGHT 1999 ACS
AN 1997:560388 CAPLUS
DN 127:214801
TI In vitro modulation of cytokine, cytokine inhibitor, and prostaglandin E release from blood mononuclear cells and synovial fibroblasts by antirheumatic drugs
AU Seitz, Michael; Loetscher, Pius; Dewald, Beatrice; Towbin, Harry; Baggiolini, Marco
CS Department of Rheumatology, University Hospital and Theodor-Kocher-Institute, University of Berne, Bern, CH-3010, Switz.

SO J. Rheumatol. (1997), 24(8), 1471-1476
CODEN: JRHUA9; ISSN: 0315-162X
PB Journal of Rheumatology Publishing Co. Ltd.
DT Journal
LA English
AB This study to assessed the effect of various antirheumatic drugs on cytokine, cytokine inhibitor, and prostaglandin E (PGE) prodn. by normal blood mononuclear cells (MNC) and rheumatoid arthritis (RA) synovial fibroblasts in vitro. MNC from healthy donors and RA synovial fibroblasts were preincubated with or without prostaglandin E2 (PGE2), indomethacin, dexamethasone, **gold** sodium thiomalate (GSTM), methotrexate (MTX), and cyclosporin A (CyA), and then cultured in the absence or presence of interleukin-1.beta. (IL-1.beta.) or **tumor necrosis factor** -.alpha. (**TNF**-.alpha.) for 48 h MCP-1. We characterized cytokines such as IL-1.beta., IL-8, monocyte chemoattractant protein-1 (MCP-1), and cytokine inhibitors such as IL-1 receptor antagonist (IL-1ra) and sol. TNF receptors (sTNFR p55 + p75) as well as PGE in the cell-free culture supernatants. In MNC and synovial fibroblast cultures dexamethasone, GSTM, and PGE2 most markedly downregulated spontaneous and/or cytokine stimulated prodn. of IL-1.beta., IL-1ra, IL-8, and MCP-1, whereas sTNFR shedding was not affected. In contrast, MTX and CyA had only marginal or no effects on mediator release, whereas indomethacin inhibited only PGE prodn. Among several antirheumatic drugs examd., dexamethasone and GSTM exhibited the most potent inhibitory effects on inflammatory cytokine and cytokine inhibitor prodn. by blood mononuclear cells and synovial fibroblasts. These drugs may exert their antiinflammatory actions by unspecific suppression of monocyte and fibroblast secretory function.

L13 ANSWER 5 OF 17 CAPLUS COPYRIGHT 1999 ACS
AN 1997:536238 CAPLUS
DN 127:214798
TI In vitro effect of **gold** sodium thiomalate and methotrexate on **tumor necrosis factor** production in normal healthy individuals and patients with rheumatoid arthritis
AU Yadav, Rajwardhan; Misra, Ramnath; Naik, Sita
CS Department of Immunology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, 226014, India
SO Int. J. Immunopharmacol. (1997), 19(2), 111-114
CODEN: IJIMDS; ISSN: 0192-0561
PB Elsevier
DT Journal
LA English
AB We studied the in vitro action of gold sodium thiomalate (GSTM) and methotrexate (MTX) on spontaneous and lipopolysaccharide (LPS) stimulated TNF.alpha. prodn. by peripheral blood mononuclear cells (PBMC) of patients with rheumatoid arthritis (RA) and normal healthy

individuals. GSTM and MTX (10 .mu.g) each were added to the cultures of PBMC either in medium alone (spontaneous) or in the presence of 10 .mu.g of LPS. GSTM and MTX augmented spontaneous TNF.alpha. prodn. in normal individuals and patients with RA but did not influence LPS stimulated TNF.alpha. prodn. However, TNF.alpha. prodn. by the PBMC of normal individuals was inhibited if the PBMC were stimulated with LPS, for 6 or 12 h, washed to remove LPS and subsequently incubated with GSTM. These data indicate that GSTM can inhibit TNF.alpha. prodn. when the PBMC are preactivated by LPS.

L13 ANSWER 6 OF 17 CAPLUS COPYRIGHT 1999 ACS
AN 1997:47667 CAPLUS
DN 126:126645
TI Immunophenotyping of gold-treated and activated peripheral blood mononuclear cells: Differential expression of cytokine receptors
AU Ibrahim, M. A. A.; Vint, I. A. M.; Foreman, J. C.; Chain, B. M.; Katz, D. R.
CS UK
SO Leucocyte Typing V: White Cell Differ. Antigens, Proc. Int. Workshop Conf., 5th (1995), Meeting Date 1993, Volume 2, 1969-1971. Editor(s): Schlossman, Stuart F. Publisher: Oxford University Press, Oxford, UK.
CODEN: 63WDAC
DT Conference
LA English
AB It appears that the antiarthritic action of auranofin may be mediated not only through its inhibitory effect on interleukin-2 (IL-2) secretion, but also through modulation of cytokine receptors, either upward in the case of the suppressive cytokine IL-10, or downward, as seen with expression of the receptors for stimulatory cytokines, e.g. TNF and IL-2. Thus, the actions of Au compds., such as auranofin, are of a more general immunosuppressive nature than has previously been suggested, and are dependent upon the functional characteristics of the target cells.

L13 ANSWER 7 OF 17 CAPLUS COPYRIGHT 1999 ACS
AN 1996:178561 CAPLUS
DN 124:249282
TI Effects of antirheumatic agents on cytokines
AU Barrera, Pilar; Boerbooms, Agnes M.Th.; van de Putte, Leo B.A.; van der Meer, Jos W.M.
CS Department of Rheumatology, University Hospital Nijmegen, Nijmegen, 6500 HB, Neth.
SO Semin. Arthritis Rheum. (1996), Volume Date 1996, 25(4), 234-53
CODEN: SAHRBF; ISSN: 0049-0172
DT Journal; General Review
LA English
AB A review with 187 refs. A review of the literature concerning the effects of traditional antirheumatic drugs on cytokines and the

cytokine and anticytokine approaches already used in the therapy of rheumatoid arthritis (RA) is presented. Many antirheumatic drugs are capable of cytokine modulation in vitro. Corticosteroids inhibit the transcription of a broad spectrum of genes including those encoding monocyte, T cell-derived cytokines and several hemopoietic growth factors, whereas drugs such as cyclosporin A and D-penicillamine interfere with T cell activation more specifically by suppressing interleukin 2 (IL-2) prodn. The in vivo effects of drug therapy on cytokines in RA patients are less well established. **Gold** compds. reduce circulating IL-6 levels and the expression of monocyte-derived cytokines, such as IL-1, **tumor necrosis factor (TNF)**, and IL-6, in the rheumatoid synovium. Decreases in circulating IL-6, sol. IL-2 (sIL-2R), and TNF receptors and in synovial fluid IL-1 levels have been reported with methotrexate. Redns. in circulating IL-6 and sIL-2R concns. have also been obsd. with cyclosporin and corticosteroids, whereas azathioprine reduces IL-6 but not sIL-2R. Studies on sulfasalazine are conflicting and the in vivo effects of D-penicillamine and antimalarials have not been studied yet. Interferon-.gamma. therapy is not effective in RA but may prove a useful antifibrotic for systemic sclerosis. Colony stimulating factors improve the granulocytopenia assocd. with Felty's syndrome or drug toxicities but can induce arthritis flares and should be reserved to treat infectious complications. Promising results are being obtained with selective antagonism of TNF and IL-1 in RA, and combinations of anticytokine strategies with traditional antirheumatic drugs have been already envisaged. These should preferably be based in a broader knowledge of the effects of antirheumatic agents on the cytokine network.

L13 ANSWER 8 OF 17 CAPLUS COPYRIGHT 1999 ACS
AN 1996:10226 CAPLUS
DN 124:105960
TI Auranofin inhibits the induction of interleukin 1.beta. and tumor necrosis factor .alpha. mRNA in macrophages
AU Bondeson, Jan; Sundler, Roger
CS Department Cell and Molecular Biology, Lund University, Lund, S-221 00, Swed.
SO Biochem. Pharmacol. (1995), 50(11), 1753-9
CODEN: BCPCA6; ISSN: 0006-2952
DT Journal
LA English
AB Gold compds. are widely used in the treatment of rheumatoid arthritis, but their mechanisms of action remain unclear. We demonstrate here that auranofin (AF) (0.1-3 .mu.M), but neither the hydrophilic **gold** compds. aurothiomalate (ATM) and aurothioglucose nor methotrexate or D-penicillamine, inhibits the induction of interleukin 1.beta. and **tumor necrosis factor (TNF)** .alpha. mRNA and

protein by either zymosan, lipopolysaccharide (LPS), or various bacteria in mouse macrophages. The auranofin-mediated inhibition of the induction of TNF-.alpha. mRNA was stronger than that of interleukin (IL) 1.beta. mRNA. AF, but not the other drugs, also inhibited zymosan-induced mobilization of arachidonate. The fact that AF inhibited the induction of mRNA for both these proinflammatory cytokines, irresp. of which stimulus was used, may indicate that it affects some common signal transduction step vital to their induction.

L13 ANSWER 9 OF 17 CAPLUS COPYRIGHT 1999 ACS
AN 1995:296945 CAPLUS
DN 122:71591
TI Paradoxical derepression of collagenase gene expression by the antirheumatic gold compound aurothiomalate
AU Makino, Yuichi; Tanaka, Hirotoshi; Makino, Isao
CS Second Department of Internal Medicine, Asahikawa Medical College, Asahikawa, 078, Japan
SO Mol. Pharmacol. (1994), 46(6), 1084-9
CODEN: MOPMA3; ISSN: 0026-895X
DT Journal
LA English
AB The neutral metalloproteinase collagenase is known to be, among others, one of the key enzymes promoting joint destruction in patients with rheumatoid arthritis. Because inflammatory cytokines, e.g., interleukin-1 and **tumor necrosis factor**-.alpha., are considered to activate collagenase gene expression through activation of the transcription factor activator protein-1, the authors examd. whether the water-sol. **gold** compd. aurothiomalate (AuTM) influenced collagenase gene expression, using phorbol ester-treated human fibroblasts. AuTM did not prevent phorbol ester-mediated activation of activator protein-1 DNA-binding activity and subsequent induction of collagenase gene expression. In contrast, AuTM counteracted the repressive effects of glucocorticoids on collagenase gene expression and restored collagenase mRNA levels. The mol. target of this paradoxical AuTM action was suggested to be the glucocorticoid receptor.

L13 ANSWER 10 OF 17 CAPLUS COPYRIGHT 1999 ACS
AN 1995:182640 CAPLUS
DN 122:4704
TI Application of x-ray microanalysis to study of the expression of endothelial adhesion molecules on human umbilical vein endothelial cells in vitro
AU Tomczok, Janusz; Sliwa-Tomczok, Wanda; Klein, Christoph L.; Bittinger, Fernando; Kirkpatrick, Charles J.
CS Inst. Pathology, Johannes Gutenberg Univ., Mainz, D-55101, Germany
SO Histochemistry (1994), 102(5), 337-43
CODEN: HCMYAL; ISSN: 0301-5564

DT Journal
LA English
AB A semi-quant. procedure is described, which allows the evaluation of expression levels of endothelial cells (HUVEC) using energy dispersive X-ray microanal. (EDX). As a model 2 adhesion mols., E-selection (CD62E; ELAM-1/endothelial leukocyte adhesion mol.-1) and ICAM-1 (intercellular adhesion mol.-1; CD54), were localized by the use of the **silver**-enhancement colloidal **gold** method after stimulation of HUVEC with endotoxin lipopolysaccharide (LPS), **tumor necrosis factor** (**TNF**) or a phorbol ester (PMA). The anal. was performed in a SEM (SEM) at an accelerating voltage of 15 kV with scanned areas of 200.times.400 .mu.m. The semi-quant. data indicated that in LPS-treated groups both adhesion mols. were expressed at a significantly higher level than in all other groups ($P<0.01$). In addn., after a 4 h treatment the expression levels of E-selectin in all groups were higher compared to ICAM-1. The exptl. data from X-ray microanal. were compared with data obtained from an ELISA and similar values were found for both types of prepn. This microanal. method is relatively simple and seems to be suitable for immunogold labeling studies on different types of endothelial cells in vitro.

L13 ANSWER 11 OF 17 CAPLUS COPYRIGHT 1999 ACS
AN 1994:555369 CAPLUS
DN 121:155369
TI Tumor necrosis factor-.alpha. mRNA expression in lipopolysaccharide-stimulated rat kidney: chronological analysis of localization
AU Noiri, Eisei; Kuwata, Shoji; Nosaka, Kazuo; Tokunaga, Katsushi; Juji, Takeo; Shibata, Yoichi; Kurokawa, Kiyoshi
CS 1st Dep. Intern. Med., Univ. Tokyo, Tokyo, Japan
SO Am. J. Pathol. (1994), 144(6), 1159-66
CODEN: AJPAA4; ISSN: 0002-9440
DT Journal
LA English
AB To study the time course of lipopolysaccharide-induced prodn. of **tumor necrosis factor**-.alpha. (**TNF**-.alpha.) in the kidney, the authors utilized a highly sensitive non-radioisotopic in situ hybridization with 1-nm **gold**-conjugated anti-digoxigenin for localization of **TNF**-.alpha. mRNA expression after lipopolysaccharide administration. TNF-.alpha. mRNA expression localized by in situ hybridization showed a peak increment in proximal tubular epithelial cells and glomeruli at 2 h and returned to almost normal levels at 6 h. The intensity of the signal was much stronger in proximal tubules than in glomeruli. These findings were confirmed by the demonstration of similar kinetics in the increase of TNF-.alpha. message, measured by using amplification of the third and fourth exons of TNF-.alpha. gene by reverse transcription-polymerase chain

reaction of microdissected proximal tubular segments and isolated glomeruli. Reverse transcription-polymerase chain reaction of cultured rat mesangial and glomerular epithelial cells demonstrated that mesangial cells, not glomerular epithelial cells, were responsible for the obsd. glomerular signals.

L13 ANSWER 12 OF 17 CAPLUS COPYRIGHT 1999 ACS
AN 1994:555332 CAPLUS
DN 121:155332
TI Cultured rat hepatic sinusoidal endothelial cells express intercellular adhesion molecule-1 (ICAM-1) by tumor necrosis factor-.alpha. or interleukin-1.alpha. stimulation
AU Ohira, Hiromasa; Ueno, Takato; Shakado, Satoshi; Sakamoto, Masaharu; Torimura, Takuzi; Inuzuka, Sadataka; Sata, Michio; Tanikawa, Kyuichi
CS 2nd Department Medicine, Kurume University School Medicine, Kurume, 830, Japan
SO J. Hepatol. (1994), 20(6), 729-34
CODEN: JOHEEC; ISSN: 0168-8278
DT Journal
LA English
AB This study investigated the expression of intercellular adhesion mol.-1, a leukocyte adhesion mol., on cultured rat hepatic sinusoidal endothelial cells during stimulation with tumor necrosis factor-.alpha. or interleukin-1.alpha.. Using immunoelectron microscopy and the immunogold technique against intercellular adhesion mol.-1, **gold** particles were shown to increase significantly on the surface of sinusoidal epithelial cells treated with **tumor necrosis factor**-.alpha. (100 U/mL) or interleukin-1.alpha. (10 U/mL) for 8 h compared with unstimulated cells. In addn., semi-quant. anal. of intercellular adhesion mol.-1 on the sinusoidal endothelial cells was performed by cytofluorometer. Even without stimulation, intercellular adhesion mol.-1 was weakly expressed. However, 8 h after tumor necrosis factor-.alpha. or interleukin-1.alpha. treatment, the expression of intercellular adhesion mol.-1 on cells was increased in a dose-dependent manner. Kinetic anal. showed that the expression of intercellular adhesion mol.-1 on sinusoidal endothelial cells treated with these cytokines increased gradually from the beginning of stimulation to 24 h. These findings suggest that hepatic sinusoidal endothelial cells may mediate the direct interaction between leukocytes and sinusoidal endothelial cells by expressing leukocyte adhesion mols. such as intercellular adhesion mol.-1.

L13 ANSWER 13 OF 17 CAPLUS COPYRIGHT 1999 ACS
AN 1991:677246 CAPLUS
DN 115:277246
TI Assessment of antitumor activity of recombinant human **tumor necrosis factor** (**TNF**) in combination with chemotherapy and hyperthermia using **silver**-stained

nucleolar organizer regions (AgNORs)
AU Tanaka, T.; Ohkubo, T.; Fujitsuka, H.; Tatematsu, N.; Oka, N.; Sugie, S.; Mori, H.
CS Sch. Med., Gifu Univ., Gifu, 500, Japan
SO Cancer J. (1991), 4(3), 193-7
CODEN: CANJEI; ISSN: 0765-7846
DT Journal
LA English
AB The no. of **silver**-stained organizer regions (AgNORs) was quantified to det. whether this value is useful as a parameter of antitumor effect of immunotherapy, human **tumor necrosis factor** (**TNF**) in combination with chemotherapy (cisplatin, CDDP) and hyperthermia (H) on the VX2 carcinoma transplanted in the tongue of domestic rabbits. Intratumor administration of TNF (104 U/rabbit) and CDDP (0.2 mg/rabbit) alone resulted in 6% of TRW (treated tumor wts. on day 14/those on day 0/CRW (control tumor wts. on day 14/those on day 0), while TNF or CDDP treatment caused <50% necrosis of the tumor. Combination therapy (TNF plus CDDP plus H) showed complete response (TRW/CRW = 0%) and >95% necrosis of the tumor. The measurement of nuclear DNA content of tumor cells treated with TNF, CDDP, and/or H indicated ploidy redn. The no. of AgNORs in tumor cell nuclei according to the response of neoplastic cells to the therapy and was well correlated with 3 other parameters such as relative tumor wt., % of necrotic area, and nuclear DNA content. Thus combination therapy using TNF, CDDP, and H showed the highest antitumor effect when compared to other therapies. Mean nos. of AgNOR, as well as other parameters of antitumor effect, may reflect the antitumor effect of xenobiotics.

L13 ANSWER 14 OF 17 CAPLUS COPYRIGHT 1999 ACS
AN 1990:417642 CAPLUS
DN 113:17642
TI Effects of disease modifying antirheumatic drugs on the production of IL-1.alpha., IL-1.beta. and TNF (tumor necrosis factor) by normal monocytes and mononuclear cells in vitro
AU Wada, Tetsuya; Singu, Masasho; Ezaki, Ichiko; Nobunaga, Masashi
CS Med. Inst. Bioregul., Kyushu Univ., Fukuoka, Japan
SO Ensho (1990), 10(2), 139-40
CODEN: ENSHEE; ISSN: 0389-4290
DT Journal
LA Japanese
AB Gold sodium thiomalate (GST) markedly inhibited the prodn. of IL-1.beta. by normal mononuclear cells and normal monocytes, and slightly inhibited TNF prodn. by normal mononuclear cells. Bucillamine, a SH compd., on the other hand, inhibited TNF prodn. by mononuclear cells. These results suggest that the inhibitory effects of GST and bucillamine on the cytokine prodn. may be one of the mechanisms by which the drugs modify the tissue destruction in

rheumatoid arthritis.

L13 ANSWER 15 OF 17 CAPLUS COPYRIGHT 1999 ACS
AN 1989:205709 CAPLUS
DN 110:205709
TI Tumor necrosis factor for accelerating neovascularization of wounds
IN Leibovich, Samuel J.; Polverini, Peter J.; Shepard, H. Michael
PA Northwestern University, USA; Genentech, Inc.
SO U.S., 8 pp.
CODEN: USXXAM
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 4808402	A	19890228	US 87-56554	19870529

AB Tumor necrosis factor (TNF) is useful for accelerating the neovascularization of surgical incisions, burns, traumatized tissue, skin grafts, ulcers, and other wounds. Murine recombinant TNF-.alpha. was impregnated to bovine collagens (Hydron) and these pellets were implanted in corneas of rats. The corneas were monitored daily for ingrowth of new microvessels from the limbal vasculature toward the implants and strong and sustained growth of new capillary blood vessels was found to have extended from the corneal limbus towards the Hydron implant contg. 3.5 ng of TNF-.alpha..
IT **7440-22-4D**, **Silver**, salts
RL: BIOL (Biological study)
(wound healing accelerating compn. contg. **tumor necrosis factor** and)

L13 ANSWER 16 OF 17 CAPLUS COPYRIGHT 1999 ACS
AN 1989:147435 CAPLUS
DN 110:147435
TI Pharmacologic modulation of TNF production by endotoxin stimulated macrophages. In vitro and in vivo effects of auranofin and other chrysotherapeutic compounds
AU Evans, G. F.; Zuckerman, S. H.
CS Dep. Immunol., Eli Lilly and Co., Indianapolis, IN, 46285, USA
SO Agents Actions (1989), 26(3-4), 329-34
CODEN: AGACBH; ISSN: 0065-4299
DT Journal
LA English
AB The gold compds. auranofin, sodium aurothioamalate, and tri-Et gold phosphine inhibit various effector functions of monocyte-macrophage. Incubation with auranofin or tri-Et **gold** phosphine inhibited **tumor necrosis factor** (**TNF**) prodn. in lipopolysaccharide (LPS)-stimulated murine peritoneal macrophages. The inhibitory effect of auranofin and

triethyl gold phosphine on LPS stimulated monokine prodn. was reversible when these compds. were incubated with macrophage cultures at 0.1-0.5 .mu.g/mL. These compds. also inhibited both TNF and interleukin-1 (IL-1) prodn. by human peripheral blood monocytes. Sodium aurothiomalate at these concns. had no inhibitory effect on TNF or IL-1 prodn. Auranofin and tri-Et gold phosphine also inhibited TNF prodn. in mice when administered orally or i.p. 2 h prior to a LD of endotoxin. Serum TNF levels from Balb/c mice were reduced when animals were predosed with 1-25 mg auranofin/kg. The inhibition of TNF prodn. by activated macrophages may contribute to the therapeutic role of gold compds. in the management of chronic inflammatory disease.

IT **7440-57-5D, Gold**, compds.
RL: BIOL (Biological study)
(interleukin-1 and **tumor necrosis factor** formation by macrophages and monocytes response to anti-inflammatory)

L13 ANSWER 17 OF 17 CAPLUS COPYRIGHT 1999 ACS
AN 1988:628320 CAPLUS
DN 109:228320
TI Endocytic pathway of recombinant murine tumor necrosis factor in L-929 cells
AU Mosselmans, R.; Hepburn, A.; Dumont, J. E.; Fiers, W.; Galand, P.
CS Sch. Med., Free Univ. Brussels, Brussels, B-1000, Belg.
SO J. Immunol. (1988), 141(9), 3096-100
CODEN: JOIMA3; ISSN: 0022-1767
DT Journal
LA English
AB The fate of **tumor necrosis factor** (**TNF**) after binding to the surface of L-929 cells was followed by using murine rTNF coupled to colloidal **gold** as a probe. A time-course study using electron microscopy was performed. The results confirm previous indications obtained from biochem. studies suggesting that TNF is internalized by this cell type. They further directly show that internalization proceeds through the classical receptor-mediated endocytosis pathway, i.e., via clathrin-coated structures and endosomes before accumulation in secondary lysosomes.

=> d his l14-

(FILE 'BIOSIS, MEDLINE, EMBASE, LIFESCI, BIOTECHDS, WPIDS, CONFSCI, SCISEARCH, JICST-EPLUS, PROMT, TOXLIT, TOXLINE, DRUGU, DRUGNL, DRUGB' ENTERED AT 14:57:25 ON 22 FEB 1999)
L14 290 S L12
L15 278 S L14 NOT L9
L16 92 DUP REM L15 (186 DUPLICATES REMOVED)
L17 10 S L16 AND ADMIN?

L18 18 S L16 AND (TOXIC? OR TOXIN)
L19 24 S L17 OR L18

=> d 1-24 bib abs

L19 ANSWER 1 OF 24 BIOSIS COPYRIGHT 1999 BIOSIS
AN 1998:232812 BIOSIS
DN PREV199800232812
TI Management of rheumatoid arthritis: Ratinale for the use of colloidal metallic gold.
AU Abraham, Guy E. (1); Himmel, Peter B.
CS (1) Optimox Corporation, 2720 Monterey St., Ste 406, Torrance, CA 90503 USA
SO Journal of Nutritional & Environmental Medicine (Abingdon), (Dec., 1997) Vol. 7, No. 4, pp. 295-305.
ISSN: 1359-0847.
DT Article
LA English
AB **Gold** salts of monovalent **gold** (**AU** I) with a **gold**-sulfur ligand (aurothiolates) are the only form of **gold** currently in use for the management of rheumatoid arthritis (RA). Aurothiolates have limited success and are associated with a high incidence of side-effects. Metallic **gold** (AUo) is non-**toxic** and used extensively in dentistry. Monoatomic metallic **gold** is generated in vivo from **AU** I salts, during oxidation to trivalent **gold** (**AU** III). Monoatomic **gold** tends to form clusters of colloid particles. It is postulated that the active ingredient in aurotherapy is AUo and the side-effects are caused by **AU** III. To test this postulate, ten RA patients with long-standing erosive bone disease not responding to previous treatment were recruited from a private practice. Clinical and laboratory evaluations were performed prior to oral **administration** of 30 mg of colloidal AUo daily and thereafter weekly for 4 weeks and monthly for an additional 5 months. There was no clinical or laboratory evidence of **toxicity** in any of the patients. The effects of the colloidal **gold** on the tenderness and swelling of joints were rapid and dramatic, with a significant decrease in both parameters after the first week, which persisted during the study period The mean scores for tenderness and swelling were, respectively, for pre- and post-1 week 58.8 and 18.2 ($p < 0.01$) and 42.5 and 15.9 ($p < 0.01$). By 24 weeks of **gold** **administration**, the mean scores were ten times lower than the pre-treatment levels being, respectively, 5.4 and 3.3 for tenderness and swelling. As a group, there was a significant improvement of functional status by 24 weeks of **gold** therapy: three patients were in clinical remission and one patient's status improved from totally disabled to full-time work. Evaluated

individually, nine of the ten patients improved markedly after 24 weeks of colloidal **gold** at 30 mg/day. The cytokines interleukin-6 (IL-6) and **tumour necrosis factor** alpha (**TNF**-alpha), the immune complexes IgG and IgM, and rheumatoid factor were significantly suppressed by the colloidal **gold**. The results of this open trial in ten patients with long-standing erosive RA not responding to previous treatment support the postulate that colloidal **gold** is indeed the active ingredient in aurothiolate therapy and that the side-effects are mainly due to the **AU** III generated by oxidation of **AU** I. Colloidal AUo could become an effective and safer alternative to the aurothiolates in the management of RA patients.

L19 ANSWER 2 OF 24 BIOSIS COPYRIGHT 1999 BIOSIS
AN 1997:405556 BIOSIS
DN PREV199799711759
TI In vitro effect of **gold** sodium thiomalate and methotrexate on **tumor necrosis factor** production in normal healthy individuals and patients with rheumatoid arthritis.
AU Yadav, Rajwardhan; Misra, Ramnath; Naik, Sita (1)
CS (1) Dep. Immunol., Sanjay Gandhi Postgraduate Inst. Med. Sci., Lucknow 226015 India
SO International Journal of Immunopharmacology, (1997) Vol. 19, No. 2, pp. 111-114.
ISSN: 0192-0561.
DT Article
LA English
AB We studied the in vitro action of gold sodium thiomalate (GSTM) and Methotrexate (MTX) on spontaneous and lipopolysaccharide (LPS) stimulated TNF-alpha production by peripheral blood mononuclear cells (PBMC) of patients with rheumatoid arthritis (RA) and normal healthy individuals. GSTM and MTX (10 mu-g) each were added to the cultures of PBMC either in medium alone (spontaneous) or in the presence of 10 mu-g of LPS. GSTM and MTX augmented spontaneous TNF-alpha production in normal individuals and patients with RA but did not influence LPS stimulated TNF-alpha production. However, TNF-alpha production by the PBMC of normal individuals was inhibited if the PBMC were stimulated with LPS, for 6 or 12 h, washed to remove LPS and subsequently incubated with GSTM. These data indicate that GSTM can inhibit TNF-alpha production when the PBMC are preactivated by LPS.

L19 ANSWER 3 OF 24 BIOSIS COPYRIGHT 1999 BIOSIS
AN 1997:80854 BIOSIS
DN PREV199799387557
TI Metal-induced modulation of nitric oxide production in vitro by murine macrophages: Lead, nickel, and cobalt utilize different mechanisms.

AU Tian, L.; Lawrence, D. A.
CS Wadsworth Cent., Albany, NY 12201-0509 USA
SO Toxicology and Applied Pharmacology, (1996) Vol. 141, No. 2, pp. 540-547.
ISSN: 0041-008X.
DT Article
LA English
AB Macrophages (M-vphi) can be induced to produce nitric oxide (NO), which has been suggested to be important for macrophages to exercise various functions. We have previously reported that an environmental **toxicant**, lead (Pb), can significantly inhibit NO production by murine splenic M-vphi-s. Herein, eight additional metal ions, **gold** (**Au**), cadmium (Cd), cobalt (Co), chromium (Cr), copper (Cu), mercury (Hg), nickel (Ni), and zinc (Zn), were assessed. In addition to Pb, Hg and Cd significantly suppressed NO production by cytokine (interferon-gamma and **tumor necrosis factor**-alpha)-stimulated murine M-vphi-s. **Au** and Cu also were inhibitory, but less than Pb, Hg, and Cd. In contrast, Cr and Zn were not modulatory, and Ni and Co significantly enhanced NO production by cytokine-stimulated M-vphi-s. The enhancement by Ni and Co was inhibited by the arginine analog N-monomethylarginine. The metals showed different activating/inhibiting profiles when added to a cell-free (activated M-vphi lysate) NO-producing-system in which inducible NO synthase (iNOS) is already expressed. Cr, Cu, Pb, and Zn moderately suppressed iNOS, which suggests that they may directly modify enzyme or cofactor activity. Cd, Hg, Mg, Ni, or Co did not produce any significant effect on NO production by the cell-free system. Inhibition of NO production by Pb-exposed M-vphi-s was not due to decreased expression of iNOS nor limited to its modest direct inhibition of iNOS; thus, other mechanism(s) must be accountable for the efficient Pb-induced inhibition of NO production by M-vphi. Ni or Co did induce a substantial increase of iNOS protein. Overall, these observations provide additional insight into the means by which metals via inhibition or enhancement of NO production may be pathogenic, by suppression of defense mechanisms or induction of hypersensitivity, respectively.

L19 ANSWER 4 OF 24 BIOSIS COPYRIGHT 1999 BIOSIS
AN 1997:70104 BIOSIS
DN PREV199799369307
TI Management of osteoarthritis and rheumatoid arthritis: Prospects and possibilities.
AU Blackburn, Warren D. Jr.
CS Div. Immunol./Rheumatol., Univ. Ala. Birmingham, Birmingham, AL 35233 USA
SO American Journal of Medicine, (1996) Vol. 100, No. 2 PART A, pp. 24S-30S.
ISSN: 0002-9343.

DT General Review
LA English
AB Conventional drug therapy in rheumatoid arthritis (RA) has failed to control the long-term morbidity and mortality associated with RA. Similarly, drug therapy for osteoarthritis (OA) can relieve symptoms, but it is not clear that it alters progression of disease. Three classes of drugs are widely used for treatment of RA: nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and the slow-acting agents. In most patients, pharmacologic therapy is initiated with NSAIDs. These drugs can relieve symptoms but do not alter the course of the disease. The gastrointestinal and other side effects attributed to these compounds are well known. Similarly, use of corticosteroids can provide rapid pain relief to patients with RA and, if used in low doses, pose limited risk of **toxicity**. Slow-acting agents, including **gold**, D-penicillamine, and methotrexate, appear to decrease radiographic progression and improve clinical and biochemical indicators of RA. Therefore, newer treatment philosophies encourage use of slow-acting agents earlier in the course of the disease in order to prevent or diminish bone and joint erosions and destruction and other manifestations of disease progression. Drugs under investigation for the treatment of arthritis appear to exhibit disease-modifying or immunomodulating properties. Tenidap is a novel agent that possesses a dual mechanism of action: cyclooxygenase inhibition and modulation of cytokine activity. In addition, several biologic agents, including antibodies to **tumor necrosis factor**-alpha (**TNF**-alpha) and to intercellular adhesion molecule-1, may prove useful. These immunotherapeutic strategies are based on knowledge of the role of cytokines in the inflammatory process in arthritis. Osteoarthritis may be managed using drug and nondrug modalities. Weight loss is especially important when OA is in the weight-bearing joints. Biopsies of synovium from patients with OA show evidence of inflammation, but whether this disease should be treated with analgesics alone or with anti-inflammatory drugs remains controversial. Other treatment modalities, including tissue transplants and cytokine-modulating drugs, are emerging for the potential therapy of OA. Surgery may also be appropriate if drug treatment fails to control symptoms.

L19 ANSWER 5 OF 24 BIOSIS COPYRIGHT 1999 BIOSIS
AN 1995:494682 BIOSIS
DN PREV199598518232
TI Quantitation and biological properties of released and cell-bound lipooligosaccharides from nontypeable Haemophilus influenzae.
AU Gu, Xin-Xing (1); Tsai, Chao-Ming; Apicella, Michael A.; Lim, David J.
CS (1) Lab. Cellular Biology, NIDCD, NIH, Building 29, Room 402, 8800 Rockville Pike, Bethesda, MD 20892 USA
SO Infection and Immunity, (1995) Vol. 63, No. 10, pp. 4115-4120.

ISSN: 0019-9567.
DT Article
LA English
AB Nontypeable Haemophilus influenzae (NTHi) is a major pathogen causing otitis media in children. NTHi releases lipooligosaccharide (LOS) as outer membrane fragments during its growth. The release of LOS may play an important role in the pathogenicity of otitis media caused by this organism. The amounts of LOS in bacterial cells and growth media for five NTHi strains were determined by quantitative **silver** staining after sodium dodecyl sulfate-polyacrylamide gel electrophoresis. These strains were estimated to have 1.6 times 10-6 to 4.8 times 10-6 LOS molecules per bacterium. During a 3-day growth period, these NTHi strains released variable but significant amounts of LOS into the growth medium. Cells started to release detectable amounts of LOS into the medium at 2 to 5 h and continued to do so for up to 48 or 72 h. The concentrations of LOS in the culture supernatants released by these five strains were 10 to 55 mu-g/ml at 24 h and 40 to 100 mu-g/ml at 72 h, which was 34 to 189% of the cell-bound LOS concentration. The biological properties of released and cell-bound LOSs from two representative strains were compared. Released LOS showed an approximately 10-fold increase in inducing human monocytes to produce **tumor necrosis factor** alpha, interleukin 1-beta, and interleukin 6, a 13- to 28-fold increase in mouse lethal **toxicity**, and a 16- to 37-fold increase in the clotting of Limulus amebocyte lysate. These results suggested that released LOS or its inflammatory mediators play a more important role than the LOS in bacteria in the pathogenicity of otitis media caused by this organism.

L19 ANSWER 6 OF 24 BIOSIS COPYRIGHT 1999 BIOSIS
AN 1994:367086 BIOSIS
DN PREV199497380086
TI Tumor necrosis factor-alpha mRNA expression in lipopolysaccharide-stimulated rat kidney.
AU Noiri, Eisei (1); Kuwata, Shoji; Nosaka, Kazuo; Tokunaga, Katsushi; Juji, Takeo; Shibata, Yoichi; Kurokawa, Kiyoshi
CS (1) First Dep. Internal Med., Univ. Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo-113 Japan
SO American Journal of Pathology, (1994) Vol. 144, No. 6, pp. 1159-1166.
ISSN: 0002-9440.
DT Article
LA English
AB To study the time course of lipopolysaccharide induced production of **tumor necrosis factor**-alpha (**TNF**-alpha) in the kidney, we utilized a highly sensitive non-radioisotopic in situ hybridization with 1-nm **gold**-conjugated anti-digoxigenin for localization of **TNF**-alpha mRNA expression after lipopolysaccharide **administration**

TNF-alpha mRNA expression localized by in situ hybridization showed a peak increment in proximal tubular epithelial cells and glomeruli at 2 hours and returned to almost normal levels at 6 hours. The intensity of the signal was much stronger in proximal tubules than in glomeruli. These findings were confirmed by the demonstration of similar kinetics in the increase of **TNF** -alpha message, measured by using amplification of the third and fourth exons of **TNF**-alpha gene by reverse transcription polymerase chain reaction of microdissected proximal tubular segments and isolated glomeruli. Reverse transcription-polymerase chain reaction of cultured rat mesangial and glomerular epithelial cells demonstrated that mesangial cells, not glomerular epithelial cells, were responsible for the observed glomerular signals.

L19 ANSWER 7 OF 24 BIOSIS COPYRIGHT 1999 BIOSIS
AN 1993:527341 BIOSIS
DN PREV199396140748
TI Improved purification and biologic activities of staphylococcal **toxic** shock syndrome **toxin** 1.
AU Kum, Winnie W. S.; Laupland, Kevin B.; See, Raymond H.; Chow, Anthony W. (1)
CS (1) Vancouver Gen. Hosp., Canadian Bacterial Diseases Network, Vancouver, BC, Canada V5Z 3J5
SO Journal of Clinical Microbiology, (1993) Vol. 31, No. 10, pp. 2654-2660.
ISSN: 0095-1137.
DT Article
LA English
AB An improved method for producing highly purified **toxic** shock syndrome **toxin** 1 (TSST-1) by preparative isoelectric focusing in a Bio-Rad Rotofor cell and then chromatofocusing is described. Purification to homogeneity was confirmed by **silver** staining after sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE; 50 mu-g of protein was loaded), by immunoblotting with polyclonal rabbit antiserum raised against the crude culture supernatant used for purification, and by autoradiography after iodination and SDS-PAGE. Biologic activity was demonstrated by mitogenicity and cytokine induction (**tumor necrosis factor** alpha (**TNF**-alpha), interleukin 1-beta (IL-1-beta), and IL-6) of human peripheral blood mononuclear cells (PBMCs) and by lethality in New Zealand White rabbits following subcutaneous infusion. In contrast to commercial TSST-1 preparations, our TSST-1 preparation required the presence of both monocytes and T cells for the induction of **TNF**-alpha and IL-1-beta from human PBMCs. A 46-kDa contaminating protein in the commercial TSST-1 preparation, identified as staphylococcal lipase, was likely responsible for the induction of **TNF** -alpha and IL-1-beta from human monocytes in the absence of T cells, a biologic activity falsely attributed to purified TSST-1. Our

improved purification procedure for TSST-1 provides a high yield and is both more rapid and less labor intensive than previously reported methods. Furthermore, our studies clearly demonstrate the need for stringent methods of purity assessment of TSST-1 preparations before ascribing to them their potent biologic activities.

L19 ANSWER 8 OF 24 BIOSIS COPYRIGHT 1999 BIOSIS
AN 1993:300486 BIOSIS
DN PREV199396018711
TI Enhancement of experimental metastasis by tumor necrosis factor.
AU Orosz, Peter; Echtenacher, Bernd; Falk, Werner; Rueschoff, Josef; Weber, Dorothea; Maennel, Daniela N. (1)
CS (1) Dep. Pathol./Tumorimmunol., Klinikum, Univ. Regensburg, F. J. Strauss-Allee, D-8400 Regensburg Germany
SO Journal of Experimental Medicine, (1993) Vol. 177, No. 5, pp. 1391-1398.
ISSN: 0022-1007.
DT Article
LA English
AB The influence of endogenous and exogenous **tumor necrosis factor** (**TNF**) on metastasis was investigated in an experimental fibrosarcoma metastasis model. A single intraperitoneal injection of recombinant humnan (rh) **TNF** or recombinant mouse (rm) **TNF** into mice 5 h before intravenous inoculation of methylcholanthrene-induced fibrosarcoma cells (CFS1) induced a significant enhancement of the number of metastases in the lung. Dose responses of rmTNF and rhTNF demonstrated a stronger metastasis-augmenting effect by rmTNF compard with rhTNF. This effect was time dependent, as **administration** of rmTNF 5 h before or 1 h but not 24 h after tumor cell inoculation caused an increase of tumor cell colony formation on the lung surface, suggesting an influence of **TNF** on the vascular adhesion and diapedesis of tumor cells. Since tumor-bearing mice showed an enhanced ability to produce **TNF** after endotoxin injection compared to control mice, tumor-bearing mice were treated with anti-mTNF antibodies. Neutralization of endogenous tumor-induced **TNF** led to a significant decrease of the number of pulmonary metastases. Histological analysis of micrometastases in the lung on day 5 by **silver** staining of proteins associated with nucleolar organizer regions revealed more metastatic foci and augmented proliferative activity of the tumor cells after rmTNF pretreatment of mice. However, no direct effect of rmTNF on the proliferation rate of tumor cells was seen in vitro. These findings suggest that low doses of endogenous **TNF** or **administered** **TNF** during cytokine therapy might enhance the metastatic potential of circulating tumor cells.

L19 ANSWER 9 OF 24 BIOSIS COPYRIGHT 1999 BIOSIS

AN 1992:351083 BIOSIS
DN BA94:43308
TI THE EFFECT OF SLOW-ACTING ANTI-RHEUMATIC DRUGS SAARDS AND COMBINATIONS OF SAARDS ON MONOKINE PRODUCTION IN-VITRO.
AU DANIS V A; FRANIC G M; BROOKS P M
CS KOLLING INST., ROYAL NORTH SHORE HOSP., ST. LEONARDS, NSW 2065, AUST.
SO DRUGS EXP CLIN RES, (1991) 17 (12), 549-554.
CODEN: DECRDP. ISSN: 0378-6501.
FS BA; OLD
LA English
AB The mode of action of slow-acting anti-rheumatic drugs (SAARDs) is complex but may often include effects of cytokine (interleukin-1, IL-1, and **tumour necrosis factor**, **TNF**) production by monocytes/macrophages. Different SAARDs. May have variable effects on cytokine production in vitro depending on the concentration of drug, the presence of other SAARDs and individual variation. The **gold** compounds **gold** sodium thiomalate (GST) and auranofin (AF) had a bimodal effect on cytokine production. High concentrations of GST (> 1 .mu.g/ml) weakly inhibited IL-1-.beta. secretion (without affecting IL-1-.alpha. or **TNF** secretion and without affecting cell-associated IL-1-.alpha. and IL-1-.beta. accumulation), and although AF (> 100 ng/ml) inhibited cytokine production it did so at concentrations near to the **toxic** range for the drug (> 200 ng/ml). GST and AF when used in combination inhibited cytokine production in a synergistic manner even at concentrations that would potentiate cytokine production if used individually. Hydroxychloroquine (HCQ) and sulfasalazine (SAP) were two other inhibitory SAARDs which acted synergistically in combination. Combination of HCQ and SAP with **gold** drugs gave variable results. D-penicillamine (D-pen) and methotrexate (MTX) were two SAARDs that generally did not affect cytokine production individually or in combination with other SAARDs. These results suggest that combination SAARD therapy may more effectively target excessive cytokine production, which is a hallmark of rheumatoid arthritis.

L19 ANSWER 10 OF 24 BIOSIS COPYRIGHT 1999 BIOSIS
AN 1989:248447 BIOSIS
DN BA87:129512
TI PHARMACOLOGIC MODULATION OF TNF PRODUCTION BY ENDOTOXIN STIMULATED MACROPHAGES IN-VITRO AND IN-VIVO EFFECTS OF AURANOFIN AND OTHER CHRYSOTHERAPEUTIC COMPOUNDS.
AU EVANS G F; ZUCKERMAN S H
CS DEP. IMMUNOL., ELI LILLY AND COMPANY, INDIANAPOLIS, INDIANA 46285, USA.
SO AGENTS ACTIONS, (1989) 26 (3-4), 329-334.
CODEN: AGACBH. ISSN: 0065-4299.

FS BA; OLD
LA English
AB The gold compounds, auranofin, sodium aurothiomalate, and triethyl gold phosphine have been demonstrated to inhibit various effector functions associated with monocyte-macrophage populations. Incubation of human peripheral blood monocytes and murine peritoneal macrophages with auranofin or triethyl gold phosphine inhibited TNF production in lipopolysaccharide [LPS] stimulated murine peritoneal macrophages. The inhibitory effect of auranofin and triethyl gold phosphine on LPS stimulated monokine production was reversible when these compounds were incubated with macrophage cultures at concentrations between 0.1-0.5 .mu.g/ml. These compounds also inhibited both TNF and IL-1 production by human peripheral blood monocytes. Sodium aurothiomalate at these concentrations had no inhibitory effect on TNF or IL-1 production. Auranofin and triethyl gold phosphine also inhibited TNF production in vivo when compounds were **administered** orally or intraperitoneally 2 hours prior to a lethal dose of endotoxin. Serum TNF levels from Balb/c mice were significantly reduced when animals were predosed with 1-25 mg/kg of auranofin. The data suggest that the inhibition of TNF production by activated macrophages may contribute to the therapeutic role of gold compounds in the management of chronic inflammatory disease.

L19 ANSWER 11 OF 24 BIOSIS COPYRIGHT 1999 BIOSIS
AN 1988:249561 BIOSIS
DN BA85:127963
TI ENHANCED PRODUCTION OF MONOKINES BY CANINE ALVEOLAR MACROPHAGES IN RESPONSE TO ENDOTOXIN-INDUCED SHOCK.
AU TABOR D R; BURCHETT S K; JACOBS R F
CS DEP. PEDIATR., UNIV. ARKANSAS MED. SCI., LITTLE ROCK, ARKANSAS 72205.
SO PROC SOC EXP BIOL MED, (1988) 187 (4), 408-415.
CODEN: PSEBAA. ISSN: 0037-9727.
FS BA; OLD
LA English
AB The enhanced production of soluble mediators by alveolar macrophages may be responsible for promoting lung injury in canines **administered** endotoxin. One of the most prominent monokines, interleukin 1 (IL-1), has the potential to significantly influence the responses of host tissues. In this study we analyzed alveolar macrophages from canines that were experimentally **administered** endotoxin (AMEC) for their ability to produce IL-1. When concentrated AMEC supernatants from in vitro cultures were incubated with fresh C3H/HEJ thymocyts, a threefold greater incorporation of [3H]thymidine resulted as compared to the response produced by controls. Heat treatment of the experimental preparations ablated this difference. Conversely, the activity of AMEC intracellular lysates did not significantly differ from the

controls. **Silver**-staining the preparations separated by SDS-PAGE revealed a low-molecular-weight species (17 kD) in the AMEC supernatant lane while a similar molecular distribution was absent in all of the control preparations examined. Moreover, using the L929 cell line in a cytolytic bioassay we found that these same AMEC supernatants also contained significantly elevated levels of **tumor necrosis factor**. Collectively, this study suggests that during endotoxin-induced canine lung injury, the alveolar macrophages generate soluble species that can substantially regulate the hosts cellular response. This activity in the canine lung may play a critical role in the development and/or maintenance of the pathology associated with exposure to endotoxin.

L19 ANSWER 12 OF 24 MEDLINE
AN 96430931 MEDLINE
DN 96430931
TI Effects of antirheumatic agents on cytokines.
AU Barrera P; Boerbooms A M; van de Putte L B; van der Meer J W
CS Department of Rheumatology, University Hospital Nijmegen, Netherlands.
SO SEMINARS IN ARTHRITIS AND RHEUMATISM, (1996 Feb) 25 (4) 234-53.
Ref: 187
Journal code: UMV. ISSN: 0049-0172.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW LITERATURE)
LA English
FS Priority Journals
EM 199702
EW 19970204
AB A review of the literature concerning the effects of traditional antirheumatic drugs on cytokines and the cytokine and anticytokine approaches already used in the therapy of rheumatoid arthritis (RA) is presented. Many antirheumatic drugs are capable of cytokine modulation in vitro. Corticosteroids inhibit the transcription of a broad spectrum of genes including those encoding monocyte, T cell-derived cytokines and several hemopoietic growth factors, whereas drugs such as cyclosporin A and D-penicillamine interfere with T cell activation more specifically by suppressing interleukin 2 (IL-2) production. The in vivo effects of drug therapy on cytokines in RA patients are less well established. **Gold** compounds reduce circulating IL-6 levels and the expression of monocyte-derived cytokines, such as IL-1, **tumor necrosis factor** (**TNF**), and IL-6, in the rheumatoid synovium. Decreases in circulating IL-6, soluble IL-2 (sIL-2R), and **TNF** receptors and in synovial fluid IL-1 levels have been reported with methotrexate. Reductions in circulating IL-6 and sIL-2R concentrations have also been observed

with cyclosporin and corticosteroids, whereas azathioprine reduces IL-6 but not sIL-2R. Studies on sulfasalazine are conflicting and the in vivo effects of D-penicillamine and antimalarials have not been studied yet. Interferon gamma therapy is not effective in RA but may prove a useful antifibrotic for systemic sclerosis. Colony stimulating factors improve the granulocytopenia associated with Felty's syndrome or drug **toxicities** but can induce arthritis flares and should be reserved to treat infectious complications. Promising results are being obtained with selective antagonism of **TNF** and IL-1 in RA, and combinations of anticytokine strategies with traditional antirheumatic drugs have been already envisaged. These should preferably be based in a broader knowledge of the effects of antirheumatic agents on the cytokine network.

L19 ANSWER 13 OF 24 MEDLINE
AN 94348853 MEDLINE
DN 94348853
TI Application of immunogold labelling for light and electron microscopic localization of endothelial leukocyte adhesion molecule 1 (ELAM-1) on cultured human endothelial cells.
AU Tomczok J; Sliwa-Tomczok W; Klein C L; Bittinger F; Kirkpatrick C J
CS Institute of Pathology, Johannes Gutenberg University, Mainz, Germany..
SO MICRON, (1994) 25 (3) 257-66.
Journal code: B3V. ISSN: 0968-4328.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199412
AB This study describes the expression characteristics of E-selectin molecules using immunogold histochemical techniques on cultured human umbilical vein endothelial cells (HUVEC). The expression of E-selectin was induced by **tumour necrosis factor**-alpha (**TNF**-alpha, 300 U/ml), phorbol ester (PMA, 10 ng/ml) and bacterial lipopolysaccharide (LPS, 4 micrograms/ml). No expression was demonstrated on control cells. Using the **silver**-enhanced colloidal **gold** -labelling technique, at the light microscopical level, HUVEC could be distinctively subdivided into three staining types. The cell labelling index, expressed as the number of 'positively' stained cells as a proportion of all viewed cells was the highest in the LPS group. For transmission electron microscopy (TEM) the preembedding immunocytochemical staining method and embedding in epoxy resin (Agar 100) according to standard procedures was used. In TEM **gold** particles were localized in close association with the apical plasma membrane, as well as on the surface of microvillus-like projections (the latter by **TNF**-alpha

group). For high resolution scanning electron microscopy (HR-SEM) the secondary (SEI) and the backscattered electron imaging (BEI) modes were used. **Gold** particles were randomly distributed over the whole cell surface, although they appeared to be denser in the perinuclear zone. The quantitative evaluation on SE and BE viewing (the number of **gold** particles per cell area in microns 2) demonstrated the highest density of labelling in the LPS-treated group, but there was only a significant difference between LPS and **TNF**-alpha groups ($P < 0.01$, t-test). Furthermore, the ultrastructural studies indicated that treatment with substances which up-regulate E-selectin expression was not related to **toxic** cell damage or significant alterations of cellular ultrastructure.

L19 ANSWER 14 OF 24 MEDLINE
AN 85088522 MEDLINE
DN 85088522
TI Necrosin: purification and properties of a cytotoxin derived from a murine macrophage-like cell line.
AU Kull F C Jr; Cuatrecasas P
SO PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1984 Dec) 81 (24) 7932-6.
Journal code: PV3. ISSN: 0027-8424.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 198504
AB An acidic proteinaceous cytotoxin was isolated from the serum-free, cell-free supernatants of J774.1 (a murine macrophage-like line) cells that had been treated with bacterial endotoxin. Cytotoxic activity was routinely monitored using the sensitive murine tumorigenic fibroblast line L-M. The **toxin** was purified 8000-fold by ion-exchange and electrophoretic procedures. It was purified to greater than 90% homogeneity, as assessed by photometric scanning of **silver**-stained NaDodSO4/polyacrylamide gels. The specific activity of the purified **toxin** was 32,000 units/microgram. The **toxin** was composed of self-aggregating non-sulfhydryl-linked multimers of a Mr 15,000 subunit. The pI of the monomer was 4.6. The active multimeric forms, as assessed by gel filtration and assayed using L-M cells, were of Mr 70,000 and 55,000. These forms were identical to those observed both in crude supernatants and in purified fractions that had not been subjected to denaturing agents. We call these forms "holotoxins" and conclude that they are aggregates of the Mr 15,000 protein. The purified **toxin** (1-1000 pM, 0.06-60 ng/ml) was active against a random assortment of tumorigenic and normal cell lines of murine, bovine, and human origin. For example, the diploid bovine endothelial line CPAE was nearly as sensitive as the L-M

line. Similarities to other **toxic** macrophage products, lymphotoxin, and **tumor necrosis factor** are discussed.

L19 ANSWER 15 OF 24 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.
AN 96086319 EMBASE
DN 1996086319
TI Management of osteoarthritis and rheumatoid arthritis: Prospects and possibilities.
AU Blackburn Jr. W.D.
CS Division of Immunology/Rheumatology, University of Alabama,Birmingham, AL 35233, United States
SO American Journal of Medicine, (1996) 100/2 A (2A24S-2A30S). ISSN: 0002-9343 CODEN: AJMEAZ
CY United States
DT Journal; Conference Article
FS 006 Internal Medicine
031 Arthritis and Rheumatism
LA English
SL English
AB Conventional drug therapy in rheumatoid arthritis (RA) has failed to control the long-term morbidity and mortality associated with RA. Similarly, drug therapy for osteoarthritis (OA) can relieve symptoms, but it is not clear that it alters progression of disease. Three classes of drugs are widely used for treatment of RA: nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and the slow-acting agents. In most patients, pharmacologic therapy is initiated with NSAIDs. These drugs can relieve symptoms but do not alter the course of the disease. The gastrointestinal and other side effects attributed to these compounds are well known. Similarly, use of corticosteroids can provide rapid pain relief to patients with RA and, if used in low doses, pose limited risk of **toxicity**. Slow-acting agents, including **gold**, D-penicillamine, and methotrexate, appear to decrease radiographic progression and improve clinical and biochemical indicators of RA. Therefore, newer treatment philosophies encourage use of slow-acting agents earlier in the course of the disease in order to prevent or diminish bone and joint erosions and destruction and other manifestations of disease progression. Drugs under investigation for the treatment of arthritis appear to exhibit disease-modifying or immunomodulating properties. Tenidap is a novel agent that possesses a dual mechanism of action: cyclooxygenase inhibition and modulation of cytokine activity. In addition, several biologic agents, including antibodies to **tumor necrosis factor**-.alpha. (**TNF**-.alpha.) and to intercellular adhesion molecule-1, may prove useful. These immunotherapeutic strategies are based on knowledge of the role of cytokines in the inflammatory process in arthritis. Osteoarthritis may be managed using drug and nondrug modalities. Weight loss is especially important when OA is in the

weight-bearing joints. Biopsies of synovium from patients with OA show evidence of inflammation, but whether this disease should be treated with analgesics alone or with anti-inflammatory drugs remains controversial. Other treatment modalities, including tissue transplants and cytokine-modulating drugs, are emerging for the potential therapy of OA. Surgery may also be appropriate if drug treatment fails to control symptoms.

L19 ANSWER 16 OF 24 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.
AN 91239195 EMBASE
DN 1991239195
TI Assessment of antitumour activity of recombinant human **tumour necrosis factor** (**TNF**) in combination with chemotherapy and hyperthermia using **silver**-stained nucleolar organizer regions (AgNORs).
AU Tanaka T.; Ohkubo T.; Fujitsuka H.; Tatematsu N.; Oka N.; Sugie S.; Mori H.
CS First Department of Pathology, Gifu University School of Medicine, 40 Tsukasa-machi, Gifu City 500, Japan
SO Cancer Journal, (1991) 4/3 (193-197).
ISSN: 0765-7846 CODEN: CANJEI
CY France
DT Journal; Article
FS 005 General Pathology and Pathological Anatomy
016 Cancer
026 Immunology, Serology and Transplantation
030 Pharmacology
037 Drug Literature Index
LA English
SL French; Spanish; English
AB The number of **silver**-stained organizer regions (AgNORs) was quantified to determine whether this value is useful as a parameter of antitumour effect of immunotherapy, human **tumour necrosis factor** (**TNF**) in combination with chemotherapy (cisplatin, CDDP) and hyperthermia (H) on the VX2 carcinoma transplanted in the tongue of domestic rabbits. Intratumour **administration** of **TNF** (104 U/rabbit) and CDDP (0.2 mg/rabbit) alone resulted in 6% of T(RW) (treated tumour weights on day 14/those on day 0)/C(RW) (control tumour weights on day 14/those on day 0), while **TNF** or CDDP treatment caused less than 50% **necrosis** of the tumour. Combination therapy (**TNF** plus CDDP plus H) showed complete response (T(RW)/C(RW)= 0%) and more than 95% **necrosis** of the tumour. The measurement of nuclear DNA content of tumour cells treated with **TNF**, CDDP and/or H indicated ploidy reduction. The number of AgNORs in tumour cell nuclei according to the response of neoplastic cells to the therapy and was well correlated with three other parameters such as relative tumour weight, % of necrotic area and nuclear DNA content. The

results of the present study suggested that combination therapy using **TNF**, CDDP and H showed the highest antitumour effect when compared to other therapies. Mean numbers of AgNOR as well as other parameters of antitumour effect, may reflect the antitumour effect of xenobiotics.

L19 ANSWER 17 OF 24 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.
AN 85069176 EMBASE
DN 1985069176
TI Necrosin: Purification and properties of a cytotoxin derived from a murine macrophage-like cell line.
AU Kull Jr. F.C.; Cuatrecasas P.
CS Molecular Biology Department, The Wellcome Research Laboratories, Research Triangle Park, NC 27709, United States
SO Proceedings of the National Academy of Sciences of the United States of America, (1984) 81/24 I (7932-7936).
CODEN: PNASA6
CY United States
DT Journal
FS 052 Toxicology
030 Pharmacology
029 Clinical Biochemistry
LA English
AB The acidic proteinaceous cytotoxin was isolated from the serum-free, cell-free supernatants of J774.1 (a murine macrophage-like line) cells that had been treated with bacterial endotoxin. Cytotoxic activity was routinely monitored using the sensitive murine tumorigenic fibroblast line L-M. The **toxin** was purified 8000-fold by ion-exchange and electrophoretic procedures. It was purified to >90% homogeneity, as assessed by photometric scanning of **silver**-stained NaDodSO4/polyacrylamide gels. The specific activity of the purified **toxin** was 32,000 units/.mu.g. The **toxin** was composed of self-aggregating non-sulfhydryl-linked multimers of a M(r) 15,000 subunit. The pI of the monomer was 4.6. The active multimeric forms, as assessed by gel filtration and assayed using L-M cells, were of M(r) 70,000 and 55,000. These forms were identical to those observed both in crude supernatants and in purified fractions that had not been subjected to denaturing agents. We call these forms 'holotoxins' and conclude that they are aggregates of the M(r) 15,000 protein. The purified **toxin** (1-1000 pM, 0.06-60 ng/ml) was active against a random assortment of tumorigenic and normal cell lines of murine, bovine, and human origin. For example, the diploid bovine endothelial line CPAE was nearly as sensitive as the L-M line. Similarities to other **toxic** macrophage products, lymphotoxin, and **tumor necrosis factor** are discussed.

L19 ANSWER 18 OF 24 JICST-EPlus COPYRIGHT 1999 JST
AN 920230309 JICST-EPlus

TI Antirheumatic Inhibition of Interleukin-8 Investigated in Cultured Synovial Cells.
AU HIROTA KAZUHISA; AKAHOSHI TOORU; KONDO HIROFUMI
ENDO HIRAHITO
KASHIWAZAKI SADAO
CS Kitasato Univ., School of Medicine
Kitasato Univ., Faculty of Nursing
Tokyo Women's Medical College, School of Medicine, Inst. of Rheumatology
SO Kitasato Igaku (Kitasato Medicine), (1991) vol. 21, no. 6, pp. 635-639. Journal Code: Z0070A (Fig. 3, Ref. 20)
ISSN: 0385-5449
CY Japan
DT Journal; Article
LA Japanese
STA New
AB Interleukin-8(IL-8), a product associated with interleukin-1(IL-1) and **tumor necrosis factor(TNF**) in the synovial cell, is an important and undesirable mediator of inflammation and joint destruction in rheumatoid arthritis(RA). In the present study, experiments were conducted by cell culture to investigate the effectiveness of certain antirheumatic drugs in blocking the production of IL-8 at the cellular level. At various concentrations several representative agents conventionally used in the management of RA were applied to the cultured synovial cells to determine whether the drugs inhibit IL-8 production. Prednisolone(PSL) markedly inhibited the production of IL-8 at various therapeutic concentrations. However, regardless of the concentration **administered**, indomethacin, methotrexate(MTX), salazosulfapyridine(SASP), D-penicillamine(D-Pc), bucillamine and **gold** sodium thiomalate(GST) had no effect on IL-8 production by the synovial cells in vitro. These results indicate that inhibition of IL-8 production is one of the main pharmacological functions of PSL employed in the treatment of RA. (author abst.)

L19 ANSWER 19 OF 24 TOXLINE
AN 1998:158236 TOXLINE
DN FEDRIP-1998-06407618
TI Mechanisms of the Cytocidal Actions of Tumor Necrosis Factor Alpha.
AU Lynch R E
CS Department of Veterans Affairs/Medical Center, Salt Lake City, UT
Department of Veterans Affairs/Research and Development (15), 810 Vermont Ave. N.W., Washington, D.C.
NC VA 00226328
SO (1998). FEDRIP DATABASE, NATIONAL TECHNICAL INFORMATION SERVICE (NTIS).
FS FEDRIP
LA Unavailable

EM 199812

AB RPROJ/FEDRIP **TUMOR NECROSIS FACTOR**; NEOPLASMS; GENE EXPRESSION; CYTOTOXINS OBJECTIVES: The goal of this project is to identify the mRNAs selectively expressed in cultured cells in response to **tumor necrosis factor** alpha (**TNF**). A mRNA selectively enriched in **TNF**-sensitive cells in response to **administration** of **TNF** may encode a protein that executes the **toxicity** of **TNF** or, alternatively, antagonizes the **toxicity** of **TNF**. RESEARCH PLAN AND METHODS: Two complementary approaches are employed. In the first (differential display reverse transcriptase polymerase reaction, DDRTPCR) mRNAs selectively enriched in cells exposed to **TNF** are identified by a method in which the 3' ends of mRNAs are copied into cDNAs by the polymerase chain reaction (PCR), using oligo deoxythymidine-based primers for the extreme 3' end of the mRNA and random oligomers to prime synthesis upstream. The mixture of fragments of cDNAs copied from mRNAs from cells exposed or not exposed to **TNF** is then displayed by autoradiography of 33P-labeled fragments after electrophoresis in acrylamide gels. Fragments uniquely expressed in **TNF**-exposed cells will be cloned, sequenced, and used to identify mRNAs of full length in libraries of cDNAs prepared from **TNF**-exposed cells. The role of mRNAs in antagonizing or in executing the **toxicity** of **TNF** in these cells will then be assessed in cells transfected with expression vectors containing the cDNAs encoding these proteins. In the second approach mRNAs that accumulate in **TNF**-exposed cells are enriched by a form of subtractive hybridization in which fragments of cDNAs are amplified from mRNAs by PCR. The cDNAs from **TNF**-exposed cells are protected at their 3' ends by incorporation of alpha-thio deoxynucleoside triphosphates. The 3' end-protected cDNAs are then hybridized by phenol emulsion-promoted reassociation with unprotected cDNAs prepared by PCR from control cells. The hybrids containing a strand with an unprotected 3' end are degraded by sequential digestion with exonuclease 111 and the Klenow fragment of DNA polymerase I followed by exonuclease Vll. The duplexes with both strands protected at their 3' ends are reamplified by PCR for another round of hybridization with cDNAs from cells not exposed to **TNF**. After a series of cycles the cDNAs uniquely enriched in **TNF** -exposed cells and spared from exonuclease degradation are re-amplified, subcloned, and used to verify that they are derived from mRNAs selectively expressed in TNFexposed cells in a variety of ways including Northern blotting. Those that fulfill this criterion are used to identify and clone the cDNA of full length from an expression library of cDNAs prepared from **TNF**-exposed cells. The cDNAs of full length are reintroduced into **TNF** -sensitive cells to assess whether the transfected cDNA confers resistance to, or sensitivity to, **TNF**. The mechanism by

which resistance or sensitivity is conferred will then be assessed. FINDINGS: The fragments of cDNAs obtained after five rounds of subtractive hybridization have been subcloned. No discrete bands were visible in acrylamide gels stained with **silver** or in autoradiograms of sequencing gels in which the products from the last stage of subtractive hybridization were displayed. No differential expression was documented when the mixture of labeled unsubtracted cDNAs from **TNF**-exposed and unexposed cells was hybridized with randomly selected subcloned plasmid DNA. The fragments of cDNAs that were more abundant after amplification by DDRTPCR from the **TNF**-exposed cells than from their controls did not identify mRNAs expressed selectively in **TNF** -exposed cells or in their unexposed controls. These appear to have been false positives. CLINICAL RELEVANCE: Identification of fragments of cDNAs from mRNAs selectively expressed in **TNF** -exposed cells may yield a family of cDNAs that are candidates for mRNAs which, when mutated, participate in tumorigenesis. Identification of the mRNAs expressed in response to **TNF** could show how this var

L19 ANSWER 20 OF 24 DRUGU COPYRIGHT 1999 DERWENT INFORMATION LTD
AN 97-01800 DRUGU T S
TI Mechanism of action of old in the treatment of rheumatoid arthritis.
AU Burmester G R; Barthel H R
CS Univ.Berlin-Humboldt
LO Berlin, Ger.
SO Z.Rheumatol. (55, No. 5, 299-306, 1996) 8 Fig. 3 Tab. 21 Ref.
CODEN: ZRHMBQ ISSN: 0340-1855
AV Abteilung fuer Rheumatologie und Immunologie, Medizinische Klinik III der Alexander-von-Humbolt-Universitaet Universitaetskrankenhaus Charite Schumannstrasse 20-21, 10117, Berlin, Germany.
LA English
DT Journal
FA AB; LA; CT
FS Literature
AN 97-01800 DRUGU T S
AB This review first describes the pathogenesis of rheumatoid arthritis (RA) and then the chemistry of the gold preparations currently used in Germany for RA - injectable aurothiomalate and aurothioglucose and orally **administered** auranofin. The distribution of gold is discussed together with its effects on adhesion molecules, blood vessels and enzymes. The mechanism of gold's side-effects, which relates to its immunogenic rather than **toxic** properties is also described. The therapeutic action of gold in RA is due to a variety of effects on the immune system which alter the processing of antigenic proteins and result in a normalization of certain disorders coupled with inhibition of collagenases and other proteolytic enzymes.

Searcher : Shears 308-4994

ABEX Aurothiomalate and aurothioglucose must be given i.m. due to insignificant oral absorption. Some 25% of orally **administered** auranofin is absorbed. After absorption, the **gold** atom is cleaved and can then react with sulphur-containing aminoacids in serum proteins. On long-term treatment, **gold** accumulates in the lymphocytes, especially the macrophages or "aureosomes" of central importance in RA. Liver, bone marrow and spleen also contain substantial amounts of **gold**, whereas levels in synovial tissue and cartilage are far lower. **Gold** normalizes T-cell anergy and Ig synthesis by B-lymphocytes. Inflammatory parameters such as ESR and C-reactive protein also fall. Monovalent **gold** inhibits antigen processing by macrophages and also their production of inflammatory cytokines such as interleukin (IL)-1 and IL-6 and **tumor necrosis factor**-alpha.

Gold also reduces the number of macrophages and reduces the expression of adhesion molecules such as endothelial leukocyte adhesion molecule-1 and the budding of new blood vessels (antiangiogenic effect) in the pannus. Through its reduction in inflammatory cytokines, **gold** indirectly inhibits the activation of collagenases and other proteolytic enzymes. A direct inhibitory effect is also present through interference with disulfide bridges. Part of **gold**-I is oxidized in macrophagic lysosomes to **gold**-III, which binds to different protein structures. The allergic effects of **gold** have been attributed to the resulting abnormal, HLA-dependent peptides which act as antigens. (JH/S54) Wirkmechanismen von **Gold** bei der Behandlung der rheumatoiden Arthritis.

L19 ANSWER 21 OF 24 DRUGU COPYRIGHT 1999 DERWENT INFORMATION LTD
AN 96-19061 DRUGU T E S
TI Management of osteoarthritis and rheumatoid arthritis: prospects and possibilities.
AU Blackburn W D
CS Univ.Alabama
LO Birmingham, Ala., USA
SO Am.J.Med. (100, No. 2A, 24S-30S, 1996) 4 Fig. 1 Tab. 47 Ref.
CODEN: AJMEAZ ISSN: 0002-9343
AV Division of Immunology/Rheumatology, University of Alabama at Birmingham, Birmingham, Alabama 35233, U.S.A.
LA English
DT Journal
FA AB; LA; CT
FS Literature
AN 96-19061 DRUGU T E S
AB The management of osteoarthritis and rheumatoid arthritis is reviewed with respect to prospects and possibilities. Drugs mentioned include: prednisone, gold, methotrexate, auranofin, D-penicillamine, hydroxychloroquine, sulfasalazine, azathioprine,

tenidap, intercellular adhesion molecule-1 (ICAM-1) and antibodies to TNF-alpha, piroxicam, diclofenac, naproxen, ibuprofen and acetaminophen (paracetamol). Side-effects of these drugs are discussed. The impact of new treatment schemes is not clear, but on the near horizon are new drugs, designed in closer accord to what is known about the molecular basis of chronic inflammation and tissue degradation and synthesis.

ABEX Conventional drug therapy in rheumatoid arthritis (RA) has failed to control the long-term morbidity and mortality associated with RA. Similarly, drug therapy for osteoarthritis (OA) can relieve symptoms, but it is not clear that it alters progression of disease. 3 Classes of drugs are widely used for treatment of RA: NSAID, corticosteroids, and slow-acting agents. In most patients, pharmacologic therapy is initiated with NSAIDs. These drugs can relieve symptoms but do not alter the course of the disease. Similarly, use of corticosteroids can provide rapid pain relief to patients with RA and, if used in low doses, pose limited risk of **toxicity**. Slow-acting agents, including **gold**, D-penicillamine, and methotrexate appear to decrease radiographic progression and improve clinical and biochemical indicators of RA. Newer treatment philosophies encourage use of slow-acting agents earlier in the course of the disease in order to prevent or diminish bone and joint erosions and destruction and other manifestations of disease progression. Drugs under investigation for the treatment of arthritis appear to exhibit disease-modifying or immunomodulating properties. Several biologic agents, including antibodies to **tumor necrosis factor** and to ICAM-1 may prove useful. These immunotherapeutic strategies are based on knowledge of the role of cytokines in the inflammatory process in arthritis. Osteoarthritis may be managed using drug and nondrug modalities. Weight loss is especially important when OA is in the weight-bearing joints. (LAJ)

L19 ANSWER 22 OF 24 DRUGU COPYRIGHT 1999 DERWENT INFORMATION LTD
AN 94-10532 DRUGU P
TI Reduction in Intensity of Pneumocystis carinii Pneumonia in Mice by Subcutaneous **Administration** of Granulocyte -Macrophage Colony Stimulating Factor.
AU Mandujano J F; D'Souza N B; Nelson S; Beckerman R C; Summer W R; Shellito JE
CS Univ.Louisiana-State; Univ.Tulane
LO New Orleans, Louisiana, United States
SO Clin.Res. (41, No. 4, 807A, 1993)
CODEN: CLREAS ISSN: 0009-9279
AV Section of Pulmonary and Critical Care Medicine, Louisiana State University, New Orleans, LA, U.S.A.
LA English
DT Journal
FA AB; LA; CT

Searcher : Shears 308-4994

FS Literature
AN 94-10532 DRUGU P
AB The in-vivo effect of s.c. granulocyte-macrophage colony stimulating factor (GM-CSF) in Pneumocystis carinii pneumonia (PCP) was investigated in mice. The Authors hypothesized that GM-CSF therapy would decrease the intensity of infection in mice with PCP by up-regulating alveolar macrophage (AM) function. They tested this hypothesis in mice depleted of CD4+ lymphocytes with a monoclonal antibody and inoculated intratracheally with P. carinii (Pc). In-vitro production by lavaged cells of tumor necrosis factor (TNF) and release of nitrite in response to gamma interferon and endotoxin (LPS) was monitored. GM-CSF therapy reduces the intensity of PCP, in part through enhanced AM capacity to produce TNF. (congress abstract).
ABEX 4 Wk after Pc inoculation, GM-CSF mice received 5 ug/day of GM-CSF by s.c. injection; control animals received the same volume of PBS. After 1 wk of treatment, animals were sacrificed and lung tissue examined for intensity of PCP (**silver** methenamine stain) and inflammation (H and E stain). Lavaged cells were also cultured in-vitro for 48 hr with/without gamma-interferon and LPS to stimulate release of **tumor necrosis factor** (**TNF**) and nitrite. GM-CSF therapy significantly decreased intensity scores of PCP in comparison to control mice (1.88 +/- 0.21 vs. 3.06 +/- 0.12). Inflammation scores were lower in the GM-CSF treated group than control, although not statistically significant (1.83 +/-0.47 vs. 2.83 +/- 0.67). Total BALF cell count and differential did not differ in either group. However, AM from GM-CSF mice released significantly more **TNF** in-vitro when compared to control after stimulation with LPS (2.65 +/- 0.30 vs. 1.45 +/- 0.26 ng/ml) and LPS + gamma-interferon (4.16 +/-0.51 vs. 2.25 +/-0.34 ng/ml). BAL cells from both GM-CSF and control mice released equivalent concentrations of nitrite in-vitro. (E54/RSV)

L19 ANSWER 23 OF 24 DRUGU COPYRIGHT 1999 DERWENT INFORMATION LTD
AN 92-10948 DRUGU T E
TI Interaction(s) Between Essential Fatty Acids, Eicosanoids, Cytokines, Growth Factors and Free Radicals: Relevance to New Therapeutic Strategies in Rheumatoid Arthritis and Other Collagen Vascular Diseases.
AU Das U N
LO Hyderabad, India
SO Prostaglandins Leukotrienes Essent.Fatty Acids (44, No. 4, 201-10, 1991) 1 Fig. 93 Ref.
CODEN: PLEAEU ISSN: 0952-3278
AV Dept. of Medicine, The Nizam's Institute of Medical Sciences, Punjagutta, Hyderabad, 500482, India.
LA English
DT Journal

Searcher : Shears 308-4994

FA AB; LA; CT
FS Literature
AN 92-10948 DRUGU T E
AB The therapeutic potential of drugs which modify interactions between essential fatty acids (EFA), eicosanoids, cytokines, growth factors and free radicals in rheumatoid arthritis (RA) and other collagen vascular diseases is reviewed. Gamma-linolenic acid (GLA), dihomogamma-linolenic acid (DGLA), eicopentaenoic acid (EPA), transforming growth factor-beta (TGF-b), dexamethasone (DX), pentoxyfylline (PF), 1,25-dihydroxycholecalciferol (1,25-diOHD3) and cyclosporin A (CY) have antiinflammatory effects via blockade of interleukin-1 (IL1) and TNF production, are relatively non-**toxic**, and may be beneficial in RA, SLE and glomerulonephritis. A plan of treatment, combined with NSAID and disease modifying drugs (chloroquine, D-penicillamine, gold, sulfasalazine and methotrexate (MX) is proposed.
ABEX **Tumor necrosis factor (TNF**), IL1, IL6 and colony stimulating factor-1 (CSF-1), IFN, PGE2, LTB4, platelet activating factor-2 (PAF) and free radicals have proinflammatory effects. EFA, DX, vitamin D3, CY and PE inhibit IL1, IL2 and **TNF** synthesis, and may prevent RA progression. TGF-b also regulates immune function and inhibits processes important in rheumatoid joint destruction. Fish oil supplementation (with DHA and EPA) or GLA can improve psoriasis, RA and SLE (low GLA, EPA and DGLA). These patients may be more susceptible to proinflammatory effects of PG and LT products of arachidonic acid (AA). GLA and EFA appear to protect bone marrow and liver from the effects of cytotoxic drugs. Thus, combinations of EFA, NSAID and disease modifying drugs are appropriate: aspirin, phenylbutazone, **gold** salts, piroxicam for acute inflammation, chloroquine, d-penicillamine, **gold** salts, sulfasalazine, hydroxychloroquine to induce remission, CY to suppress IL-2 synthesis, with possible potentiation and prevention of osteoporosis by vitamin D3, PE to block **TNF** production, suppress free radical synthesis and improve microcirculation by increased RBC deformation, EFA for inhibition of inflammation, **TNF**, IL1, IL2 and PAF, increased formation of PGE1, PGI and endothelium-derived growth factor, protection of tissues from cyclophosphamide or MX, steroids (patients with little morbidity and osteoporosis), low dose MX (with protection by polyunsaturated fatty acids) and TGF-b. A preliminary study in 6 patients shows EFA (GLA/EPA), PE, 1-alphahydroxycholecalciferol, NSAID, chloroquine plus sulfasalazine for 1 yr is well tolerated, effective and almost free of side-effects. (E8/SL)

L19 ANSWER 24 OF 24 DRUGU COPYRIGHT 1999 DERWENT INFORMATION LTD
AN 89-48765 DRUGU P S
TI Bimodal Effect on Gold on IL-1 Production by Blood Monocytes.

08/966940

AU Danis V A; Kulesz A; Nelson D S; Brooks P M
LO Sydney, Australia
SO J.Rheumatol. (16, No. 8, 1160-61, 1989) 2 Fig. 10 Ref
CODEN: JRHUA9 ISSN: 0315-162X
AV The University of Sydney, Royal North Shore Hospital, NSW 2065, Australia.
LA English
DT Journal
FA AB; LA; CT
FS Literature
AN 89-48765 DRUGU P S
AB In human monocytes in culture, in the presence of ind gold Na thiomalate (GT) and auranofin (AF) at low con potentiated lipopolysaccharide (LPS)-induced interleu production, while at higher concentrations IL-1 produ inhibited, as reported in a letter. There was wide i variation. Since it takes several mth to attain maxi levels, the low concentrations at the beginning of th conceivably potentiate IL-1 production and cause tran exacerbation or at least contribute to the delayed cl response to gold.
ABEX Blood monocytes from 10 healthy subjects were culture presence of 1 uM IN; GT was used at 1-1000 ng/ml and 0.1-500 ng/ml. Low concentrations of GT and AF poten LPS-induced IL-1 production 2-6 fold, while higher co were inhibitory. There was a very wide range of conc which either effect ocurred in different subjects. T potentiation and inhibition overlapped. There was al different subjects, a very wide range of ratios of 50 concentrations to optimum potentiating concentrations than 100 in the case of GT and 5-200 for AF. GT and bimodal effects on IL-1 secretion induced by serum co rheumatoid factor, or by such serum, or LPS, acting s with **tumor necrosis factor** alpha or interferon gamma. Inhibition was not due to **toxicity** the **gold** compounds, as viability was affected only by highest concentrations (reduced from 80-73% for GT an and then to a lesser extent than was IL-1 secretion (reduction). (KD)

=> fil hom